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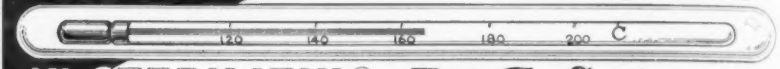

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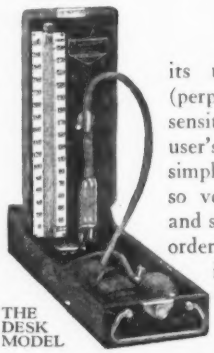

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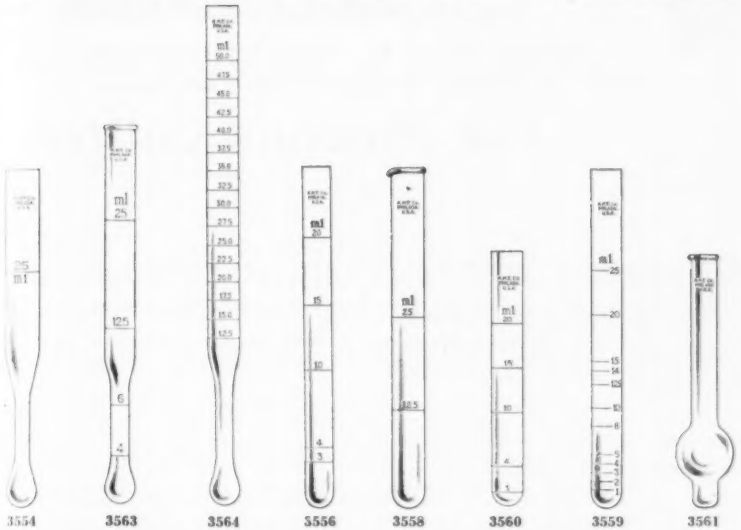

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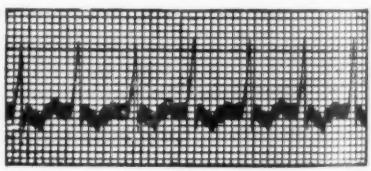

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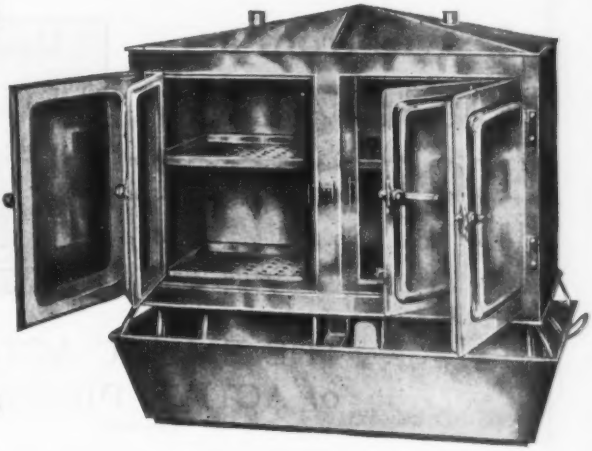

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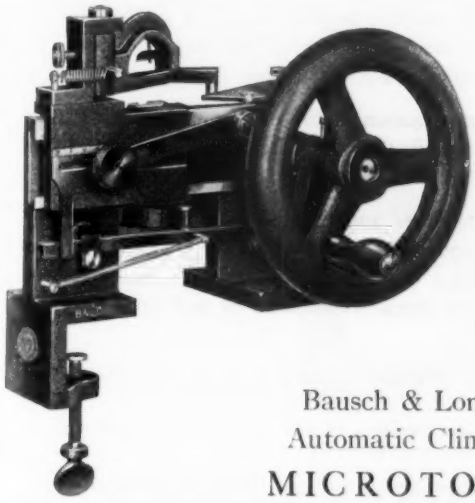

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No. VII

By. F. A. Upsher Smith, Ph. C.

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(Continued)

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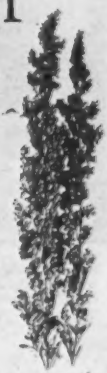

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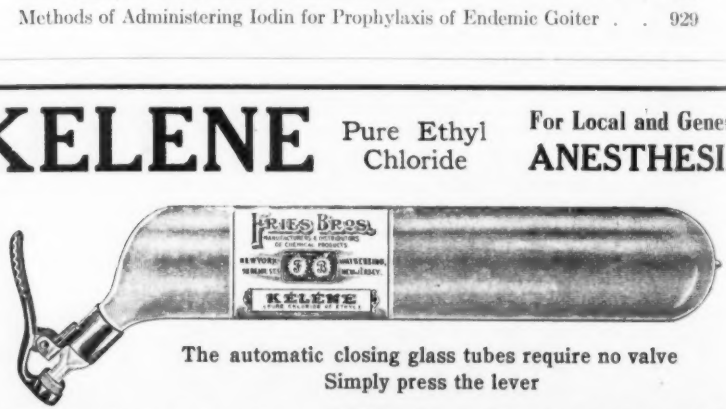

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OF THE MEDICAL SCIENCES

JUNE, 1924

ORIGINAL ARTICLES.

CLINICOPATHOLOGICAL STUDY OF A SERIES OF CASES OF ACUTE MENINGO-ENCEPHALITIS.*

By Quinter O. Gilbert, M.D.,
OAKLAND, CALIF.,
AND
Adeline E. Gurd, M.D.,
ANN ARBOR, MICH.

During recent years an abundant literature has accumulated dealing with the disease Lethargic Encephalitis. Few of the contributions that have appeared have concerned themselves with detailed studies of the histopathology of the disorder or the problems of differential diagnosis. With this in mind we have made a study of a selected number of fatal cases of various forms of acute meningo-encephalitis, in order to contribute to the differential diagnosis of these disorders and to direct attention to some clinical errors that have come to our notice, where laboratory studies and post-mortem examinations have not been used to confirm the diagnosis.

Further, a correct understanding of the underlying pathological changes in the central nervous system may aid in a better knowledge of the late clinical manifestations that are now of such importance in the care of residual effects of this disorder.

During the spring months of 1920, there occurred in the vicinity of Detroit a considerable epidemic of lethargic encephalitis. In all there were about 100 cases. During this time there came into

* The clinical observations were made in the medical division of the Receiving Hospital, Detroit, Mich. The pathological studies are by Dr. Gurd, laboratory of Neuropathology, State Psychopathic Hospital, Ann Arbor, Mich.

the Receiving Hospital a considerable number of acute cases of cerebral disorder of various types usually in extremis, or when the disease was well advanced. A selected series of these cases in which autopsies were obtained forms the basis of this contribution. The autopsy in all cases was made a few hours after death.

The brains were fixed in 10 per cent formalin and at once sent to the laboratory of neuropathology, at the State Psychopathic Hospital, Ann Arbor, Mich., where they were studied by Dr. Gurd. The results of the histopathological studies are given in connection with the presentation of each case and are summarized at the conclusion of this contribution. The material studied was from a wide range of regions. Each region was studied in preparations following the methods of Alzheimer, Bielschowsky, Klarfeld-Achucarro, Herxheimer and Weigert. This made possible a broad survey of the various reactions in specific tissues in a very complete way.

Case I.—S. G., male, aged thirty-one years, was admitted in a semicomatose condition with signs of meningeal irritation. The only information available was that for several weeks he had been sick with fever, headache and general weakness, but had kept at work until a week ago. Four years previously while in the Greek Army he had both gonorrhea and syphilis. Examinations showed him to be under-nourished and considerably dehydrated. The chest showed a definite impairment of both upper lobes with broncho-vesicular breathing and increased moisture throughout the lung area. His temperature (rectal) varied during his illness between 99° and 103°; pulse-rate ranged between 80 and 120; respirations from 20 to 40.

Neurological Examination. The pupils were unequal and did not react to direct or consensual light. The intrinsic eye muscles were normal. Accommodation could not be accurately determined. The head and neck were held rigidly. The patellar and Achilles reflexes were absent. Tests for the reflex responses of Babinski, Oppenheim, and Chaddock gave no reactions. None of the superficial skin reflexes could be obtained. Kernig's sign was always elicited, and there was flaccid paraplegia of the lower extremities. No response was obtained to deep pin pricks over the entire body. The urine was retained, and there was apparent loss of rectal control.

The urine showed no abnormal findings. The blood showed 13,000 white cells. The differential count was: Polymorphonuclear cells, 73 per cent; large lymphocytes, 10 per cent; small lymphocytes, 7 per cent; large mononuclear cells, 6 per cent; transitional forms, 4 per cent. Wassermann examination was negative on the blood. Two lumbar punctures were made. In both the fluid was under increased pressure. There were at the first examination 260 cells and at the second 200 cells. There was a strong ++++ globulin reaction (Pandy). The curve of the mastic test at one examination

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was 221100. The cells were nearly all of the large mononuclear type, and many showed marked ameboid movements.

At the second lumbar puncture he was given a reinjection of mercurialized serum, and an intravenous injection of 0.4 gm. of arsphenamine. There was a slight improvement for one day, after which he relapsed into unconsciousness. The eyes were rolled upward with slight divergent strabismus.

Autopsy. Examination of the brain showed adherent dura mater and marked congestion of the small vessels of the pia mater. No tubercles were observed in the gross inspection. The lungs showed old tubercular infiltration with caseation in both upper lobes. The remaining organs showed no marked gross abnormalities.

Microscopical Examination. Lungs showed an old thickening of the pleuræ with infiltration of both lungs by active tubercle formation of varying size and age. The liver showed increase in fibrous tissue with diffuse congestion. The kidneys showed marked congestion with a moderate grade of chronic nephritis.

Central Nervous System. Gross inspection of the brain after several weeks hardening in 10 per cent formalin solutions showed marked injection of the meningeal vessels. The pia-arachnoid was turbid, especially over the sulci. The lateral ventricles were widely dilated. The choroid plexuses of the lateral ventricles were cystic and calcareous. The ependyma of the fourth ventricle was coarsely granular.

Microscopical study showed all portions of the pia-arachnoid involved in a meningitic process, tubercular in type, characterized by a dense infiltration by small lymphocytes, plasma cells, polyblasts and macrophages, occasional giant-cells containing from 2 to 25 nuclei and tubercle bacilli in many areas. Very little connective-tissue increase was observed. Here and there the inflammatory process assumed an irregular round "tubercle" form.

The bloodvessels showed no alteration of either adventitial or elastic coats. The endothelial cells showed some swelling at times, but more commonly shrinking and detachment from the vessel wall. The adventitial lymph spaces of the meningeal vessels were much distended and packed with plasma and lymphocytic cells. This infiltration followed the vessels of the pia into the cortex for a very limited distance, becoming gradually lessened in density until it disappeared. The capillaries and deeper cortical vessels showed no infiltration. The meningitis was much more severe in the medulla and pons, and the infiltration of the adventitial lymph spaces of the vessels continued into the substance of the medulla and pons to a very considerable distance and many small inflammatory foci were seen at a distance from the surface; *e. g.*, foci were noted in the olives, in the third nerve nuclei and in the lenticular nuclei.

The ependyma of the third ventricle, the aqueduct of Sylvius and of the fourth ventricle showed much proliferation and the inflammatory process in many areas had invaded the subependymal regions, occasionally forming foci of some extent in both thalami and caudate nuclei. Many portions of the choroid plexes showed inflammatory infiltration by plasma cells and small lymphocytes.

A very marked glial reaction was observed in the molecular layer of the cortex near infiltrated vessels wherever they passed into the nerve tissues and in the neighborhood of the inflammatory foci noted in the lenticular nuclei, medulla, etc. The majority of the proliferating cells showed much increase in the size of the fibers and the nuclei were already undergoing regressive changes, the nuclei being small, pyknotic and irregular in form. An occasional ameboid cell was seen. No rod cells were observed.

The cortical nerve cells showed, in general, acute swelling, but many were in a more advanced state of degeneration, some in complete disintegration. Many of the smaller pyramidal cells were dark and turbid in hue, the nuclei also being of the same color. The protoplasm was broken up into granules. The nuclear membranes were either jagged and irregular or indistinguishable from the surrounding protoplasm.

Small hemorrhages were seen in the pons, and diapedeses in the basal ganglia.

Pathological Diagnosis. Chronic tuberculosis of lungs; congestion of kidneys; moderate chronic nephritis; mild cirrhosis of liver; acute tubercular leptomeningitis; infiltration of cortical vessels of a chronic inflammatory type; multiple tubercular encephalitic lesions in basal nuclear structures; chronic inflammatory reactions of choroid plexuses; perivascular progressive glia reactions in the cortex; degeneration of nerve cells of cortex of the type of acute swelling; multiple miliary hemorrhages in the pons.

Case II.—S. C., male, aged twenty-seven years. Two weeks prior to admission the patient noticed pains in the left shoulder and arm. This subsided until two days before coming to the hospital, when there developed an acute onset with fever, drowsiness, diplopia and pains in the left arm with muscular twitchings about the lower thorax and upper abdomen.

On examination the patient lay in bed in a lethargic state. When aroused he attempted to answer questions, but his responses were slow. He was conscious of having wet the bed on the night previous. The lungs were negative; the heart showed a slight left-sided hypertrophy with accentuation of the second aortic sound. The abdomen was negative except for slight suprapubic fulness. His blood-pressure was 175/100.

Neurological Examination. The pupils were contracted, reacting sluggishly to light and accommodation. Both eyelids drooped, but

could be elevated voluntarily by wrinkling the forehead. No extra ocular muscular change was present; no facial paralysis. Biceps and triceps reflexes were present. Umbilical and cremasteric reflexes questionable. The patellar reflex was lost, but the Achilles was present. The Gordon and Oppenheim tests produced no response; Babinski's and Chaddock's reactions were absent, but plantar stimulation caused a marked tremor of the lower extremities. There was more or less constant contraction and twitching of the abdominal muscles which was somewhat less marked in the arms. There was no paralysis, Kernig, or rigidity of the neck. It was necessary to catheterize the urinary bladder.

Two days later the pupils were much contracted. There was no response to light nor to tests for accommodation. The patellar, Achilles, biceps, umbilical, epigastric and cremasteric reflexes were lost. There was a bilateral external rectus palsy. Twitchings of the thoracic and abdominal muscles together with a "diaphragmatic jerk" were present. No response could be obtained to stimulation of the soles of the feet. Questions were answered very incoherently and in an unclear manner.

Two days after the above examination, the patient voluntarily called for a urinal and mentally was much clearer. Neurologically, however, there was no definite change. Three days later, the patient was still much clearer mentally, talked freely but was disoriented as to time and place. He said he felt as though "he was doped." He realized that he was somewhat mixed in his statements and that his memory was poor.

From this time, the patient gradually entered into a deep stupor from which he could not be aroused. When stimulated he tried to articulate but speech was inaudible. The right pupil was contracted to a pin-point, while the left was slightly larger. Neither reacted to light nor in accommodation. The biceps, triceps, umbilical cremasteric and patellar reflexes continued absent. The Achilles was present but diminished. There was involuntary bowel movement and urination.

The urine examination showed a specific gravity of 1025, a definite reaction for albumen, and the sediment showed a few granular casts.

The blood examination showed 10,000 white cells, 75 per cent polymorphonuclears, 5 per cent large lymphocytes, 11 per cent small lymphocytes, 5 per cent large mononuclears, 4 per cent transitionals. The blood Wassermann was negative. The blood incoagulable nitrogen was 0.042 gm. per 100 cc.

The spinal fluid ran freely. It was clear and contained 50 cells per c.mm. on first examination, and on a later examination 20 cells; these were small mononuclear cells. The first examination showed but a trace of globulin, the second a slightly larger amount. The Wassermann was negative. The mastic reaction was 110000.

Clinical Diagnosis. Meningo-encephalitis, lethargic; chronic nephritis.

Autopsy. Autopsy showed a marked congestion of the meninges, which were thickened and definitely adherent to the skull. The encephalon was very red, due to dilation and congestion of all the small vessels. The accessory sinuses were negative. The lungs were negative. The heart showed considerable left ventricular hypertrophy, with the aorta in good condition. The kidneys presented a granular surface when the fibrous capsule was stripped, together with secondary contraction. All other organs were negative.

Microscopical Examination. This was negative except for sclerosed glomeruli, dilation, thickening of the bloodvessel walls, and congestion in the kidneys. Otherwise there was nothing definite of note.

CENTRAL NERVOUS SYSTEM. The brain at autopsy was noted as very wet and cherry-red in color, and on later inspection it was unusually dark yellowish. The meningeal vessels were much congested and the meninges over the sulci and particularly over the base of the brain were turbid and opaque. Slight dilatation of the lateral ventricles was present.

Microscopical Examination. This showed all the bloodvessels extremely congested. Some of the large meningeal veins were thrombosed, one of which was beginning to organize. Hemorrhages into the pia-arachnoid were seen over the pons and cerebellum but no hemorrhages or diapedeses were seen in the nerve tissues in any portion examined. The adventitial coat of the vessels was unaltered, the elastic appeared somewhat swollen, the endothelium, especially of the smaller vessels and the capillaries, was swollen and in many vessels was proliferating very rapidly, but instead of remaining in place, or forming new vessels, it appeared to desquamate and lie in the lumen of the vessels, sometimes forming real thrombi. No infiltrated foci were seen in the cortex, but the medulla showed a few scattered vessels with the adventitial lymph sheaths full of small lymphocytes, plasma cells and polyblasts. The cells filled rather loosely the distended lymph spaces and did not always form complete sheaths. The caudate and lenticular nuclei also showed one or two very small inconspicuous foci. On the other hand, the pons and peduncles, including the substantia nigra, and the third nerve nuclei, were literally riddled with large and small foci of infiltrated vessels. The locus ceruleus especially contained many foci and the capillaries here showed plasma cells bordering their walls. In addition to the comparatively recent inflammatory foci many small foci were seen, which were evidently the remains of an earlier inflammatory action. In these little foci the nerve cells were partially or entirely destroyed and a mass of glia cells and fibers filled the space.

The pia-arachnoid showed no widening beyond that caused by the distended vessels. Many portions of it seemed completely normal, but over the sulci there was usually some slight cellular infiltration by small lymphocytes, an occasional plasma cell and polyblast.

The nerve cells in general were edematous, the nuclei showing folding of the nuclear membrane. A good many axonal reactions were seen, but no destroyed cells except in the areas of inflammatory foci. There was no glial proliferation in the cortex, but cells were seen here and there in both gray and white matter in regression, with very small irregular nuclei.

In the areas where more recent inflammatory foci occur there was some slight proliferation of glia cells, the nucleus being large and rather clear and the body large and pale staining. Around the foci of older date, the small scars spoken of above, both cells and fibers were increased. A good many rod cells were seen in the diseased areas of the pons and peducles.

No alterations were seen in myelin sheath or Bielschowsky's stain, except in the Alzheimer-Mann's stain which showed some myelin balls and swollen and discolored axis cylinders in the diseased areas. Many amyloid bodies were seen in the margins of the pons and peduncles.

Pathological Diagnosis. Chronic nephritis; cardiac hypertrophy; acute congestion of pia-arachnoid; endarteritis of meningeal vessels, with multiple thrombosed vessels; hemorrhages in pia-arachnoid; disseminated encephalitic foci in medulla and brain stem and diffuse and focal degenerative changes in cortex and nuclear collections; localized progressive glia reactions in regions of encephalitic areas; pathological process of lethargic encephalitis.

CASE III.—P. F., male, aged forty-nine years. The patient was conscious, but because of the involvement of the face and neck muscles in particular, he could talk but little. He stated, however, that he had been feeling ill "generally" for about three days. The day before entrance, he was awakened by a pain in the right side and lumbar region; later his jaws and neck muscles stiffened until he had to lie with his head retracted, and could barely separate his teeth when attempting to open his mouth. He had some cough, no headache, chills or vomiting. There was no history of trauma or of taking drugs.

The patient was a large, well-nourished man, lying in bed with his head retracted. He was conscious and attempted to answer questions. When the command was given to open the mouth and protrude the tongue, the tip was caught between the teeth by a spasmodic contraction of the masseter muscles.

Neurological Examination. The function of pupils and extrinsic muscles of the eyes were normal. There was a marked stiffness of the neck and lumbar muscles. There was no Chvostek. The muscles of the face and neck were tetanically spastic. The biceps, triceps and patellar reflexes were slightly increased. The Babinski was persistently present on the left side. Oppenheim and Gordon reflexes were less positive. The umbilical and cremasteric reflexes were normal. No sensory changes were found.

The lungs were negative except for rales at the base. The heart was negative except for an accentuation of the second aortic sound. The abdomen was negative to palpation. Blood-pressure 140/80. In the examination of a small specimen of sputum no tubercle bacilli were found.

The temperature varied from 99° to 100°; pulse about 100; respiration 30.

The urine examination showed nothing abnormal. The blood examination gave 16,500 white cells. The blood Wassermann was negative. The spinal fluid was under pressure, and clear; there were 300 medium sized mononuclear cells per c.mm. and a trace of globulin. The Wassermann was negative. The mastic was 110000.

The patient developed difficulty in swallowing, became cyanotic and rigid throughout the body and died within twenty-four hours.

Clinical Diagnosis. The diagnosis was uncertain. Tetanus was suggested but no definite wound of entrance was found. The changes in the spinal fluid suggested an acute meningo-encephalitis of undetermined origin.

Autopsy. The cerebrospinal fluid was much increased. The meninges were adherent to the vault of the skull; they were quite thick and slightly nodular, without evidence of hemorrhage. The brain was markedly injected. The lungs showed marked anthracosis and a few calcareous and caseating tubercles at both apices.

The heart showed considerable thickening of the edges of the mitral valves, some sclerosis of the aortic valves, marked atheromatous changes in the ascending aorta and moderate left ventricular hypertrophy. The liver showed moderate enlargement with some increase in fibrous tissue. There was some chronic exudate over the spleen surface. The kidneys showed secondary contraction and a granular surface when the capsule was stripped. There were numerous old adhesions about the cecum.

Microscopical Examination. This showed old tubercles in the lungs, fatty degeneration and atrophy of the heart muscles, epicardial infiltration with round-cells together with early aortitis. The liver showed moderate degeneration with increase in fibrous tissue. The spleen showed atrophy, increased fibrous tissue and sclerosis of many bloodvessels. The kidneys showed sclerosis of the glomeruli and the tubular epithelium.

Central Nervous System. On gross observation of the brain, an unusual slenderness of the basal vessels at once attracted attention. The internal carotids, communicating arteries and basilars appeared not more than half their usual size. Small sclerosed spots were also observed in all the basal vessels and on the branches in the fossæ Sulvii as far as they could be followed. Other agenetic features were present besides the lessened size of the bloodvessels. The Rolandic sulci cut into the Sylvian fissures, and many irregular and stellate depressions were seen at the junctions of the sulci.

Microscopical Examination. The meninges were negative. All bloodvessels were very full of blood, and occasionally a small hemorrhage was seen. The adventitial coats of most vessels were considerably thickened. The elastic layer in some of the larger vessels in the meninges of the medulla was thickened and split. Small effusions of blood were seen in the medulla and basal ganglia.

The nerve cells were all very edematous, the larger number having swollen, pale nuclei and more or less honeycombing of the body. Many cells showed Nissl's severe degeneration. In some the nuclei were dark colored and scarcely distinguishable from the rest of the cell. Large amounts of lipoid substance were present in most cells. The Betz cells and the larger pyramidal cells showed much less injury than the smaller cells and in some cases were normal. Axonal reactions were not seen. The glia cells did not seem increased in number, but many were much enlarged, but already showing regressive changes. An unusual number of "Füll-Körperchen" were seen in many areas.

Pathological Diagnosis. Pachymeningitis; chronic myocarditis; aortitis; hepatitis; sago spleen; congestion of the kidneys and moderate nephritis; chronic apical tuberculosis; agenetic anomalies in cerebral arteries, cerebral arteriosclerosis; diffuse degenerative changes in cortical nerve cells (Nissl's type of severe degeneration).

CASE IV.—Mc. M., aged twenty-eight years, laborer. Patient was brought to the hospital in an unconscious and delirious condition. No history of the past or present trouble was obtained.

The patient was a poorly-nourished negro, in a filthy condition. There were constant incoördinate movements of both arms, together with inaudible mutterings. Rotatory movements of both legs with flexion of the feet were constantly present. At times, he waved the arms about and picked at the bedclothes. There was considerable rigidity to passive movements of both arms and legs. The neck was stiff on rotation and flexed with difficulty. The left pupil was smaller than the right, neither reacted to light. The ocular muscles and accommodation could not be tested. The eyes showed no nystagmus. Both lids drooped without definite ptosis. The left corner of the mouth drooped. The biceps and triceps reflexes were questionable because of movements during the examination. The umbilical, cremasteric, patellar and Achilles reflexes were absent. Plantar stimulation caused no response. The Kernig was questionably negative. The legs, while not paralyzed, were more or less flaccid.

The lungs were hyperresonant on both sides with moist gurgling rales everywhere. The impairment was most marked over the posterior apices. The heart was negative, except for a soft systolic murmur. The abdomen was tympanitic with gas. The urinary bladder was distended. Catheterization was necessary. The tem-

perature varied from 100° to 102°. Pulse was 110 to 180 and respiration 30 to 60 at the time of death.

The urine was clear, specific gravity 1018, with a trace of albumin and a few red blood cells in the sediment.

The blood examination showed hemoglobin, 75 per cent; red blood cells, 4,000,000; white blood cells, 15,450; polymorphonuclears, 89 per cent; large lymphocytes; 4 per cent, small lymphocytes, 2 per cent; large mononuclears, 5 per cent; blood Wassermann, ++++ positive.

The spinal fluid was under pressure; globulin ++++, cells 150; large and small mononuclears with many of the larger cells showing ameboid movements. Mastic 111000. The spinal fluid Wassermann was negative.

Autopsy. The meninges were markedly congested. The spinal fluid was excessive. Small whitish areas were present over the sulci and convolutions, but they were not of definite tubercle formation. All the small vessels were much congested. The pia was elevated, due to increased fluid beneath.

The right lung showed diffuse hypostatic bronchial pneumonia with small calcareous nodules at the apex, together with small abscesses. The left lung showed congestion and small nodules in the upper lobe. The heart showed scleroses of the coronary arteries and of the mitral valves, together with an early aortitis and definite atheromatous changes in the aorta. There were caseating glands about the pancreas and spleen and extension caseation into the edge of the spleen. The kidneys showed congestion and moderate secondary contraction. Definite tubercles were seen in both the spleen and the kidneys.

The microscopical examination showed many tubercles of varying sizes and age in the lungs. The lymph glands, spleen and liver showed many tubercles, some with caseation. The heart showed some albuminous degeneration of the muscle and there was early sclerosis of the aorta.

Central Nervous System. Microscopically, the pia-arachnoid drew immediate attention. It was not much widened between sulci, but many small lymphocytes, plasma cells and small and large phagocytes (macrophages) were seen in all areas examined. Over and in the sulci the infiltration was very dense and in many places breaking down of the infiltration mass was seen, indicated by the presence of many polynuclear leukocytes scattered through the mass and especially in the center of the mass. Many tubercle bacilli were seen in these areas.

The meningitis was most severe over the medulla, pons and peduncles, and vessels passing in from the meninges in these areas frequently showed considerable infiltration by plasma cells, small lymphocytes and polyblasts for some little distance from the margin of the section.

The ependyma of the aqueduct of Sylvius and the fourth ventricle showed much proliferation in many small patches, and in some areas it was infiltrated by plasma cells, lymphocytes and polynuclear leukocytes. In the gray substance around the aqueduct occasionally a focus of infiltration was seen around vessels. Focal infiltrations were also seen on the ventricular margins of those sections of thalami and caudate that were examined, and several rather large foci were seen scattered irregularly through the caudates. The portions of lenticular nuclei examined were free from foci. No foci were observed in the cranial nerve nuclei.

The choroid plexuses from the lateral and fourth ventricles showed dense infiltration into some of the villi by plasma cells, lymphocytes and phagocytes. The infiltration followed the vessels into the villi and occupied all the tissues of the supporting connective trabeculæ and resulted in complete destruction of large numbers of the secreting cells. The plexus of the fourth ventricle was more involved than that of the lateral ventricles.

All bloodvessels were overfull with blood and occasionally there was an excess of polynuclear leukocytes and lymphocytes in their lumina. Their coats showed no alterations. The adventitial lymph spaces were much dilated and frequently packed with plasma cells and lymphocytes in the meningitis areas; especially in the small foci described above in thalami, pons, etc.

The nerve cells in the cortex were all edematous, showing folding of the nuclear membranes, and pale finely granular protoplasm. Many were much more severely altered, some appearing as fragments. Axonal reactions were rarely seen. Occasional myelin balls and swollen and discolored axis cylinders were shown by the Alzheimer-Mann's stain. The nerve fibrils were difficult to stain in Bielschowsky's stain, but when demonstrable showed slight change.

Satellitosis was increased. Both glia fibers and glia cells were in great excess in the molecular layer, where many very large proliferating cells were seen. The glia was increased to some extent in both white and gray matter aside from the molecular layer, and many ameboid cells were seen. Rod cells were seen in the cortex and also in the pons and peduncles. The nerve cells of the pons, medulla, and basal ganglia were edematous, but very few showed any severe degeneration. The subependymal glia was much increased, but proliferating cells were much smaller in size and more regular in form (small ovals) than the submeningeal glia.

Pathological Diagnosis. Chronic myocarditis; aortitis; pulmonary tuberculosis; chronic nephritis; tuberculosis of lymph glands, spleen and liver; tubercular encephalitis; granular ependymitis; tubercular meningitis; diffuse degenerative changes in nerve cells of cortex; progressive alteration in the neuroglia cells of the brain.

CASE V.—O. S., aged thirty-one years. The patient was very drowsy, mentally unclear and retarded in such a manner that a history other than that of a recent sore throat and a diplopia was unobtainable.

Examination. The patient was a well-developed male. He lay in bed stuporous or drowsy and was aroused with great difficulty. He mumbled incoherently in Polish. When stimulated by sharp commands such as, protrude the tongue, he put it first to the left then to the right with marked coarse tremors and twitchings. The arms were in almost constant motion. He often clutched both hands and had a decided tendency to pick at both the genitalia and his tongue. There was a marked drooping of the eyelids, more particularly of the right. The pupils were small and reacted sluggishly to light. The right pupil deviated to the right, while the left was centrally placed. The patient was able to elevate the eyelids when commanded to do so. Nasal and aural cavities were negative. There was no evident muscular paralysis. The neck was slightly stiff. The biceps, triceps and patellar reflexes were not obtained, Achilles slightly present. The Babinski, Oppenheim, Gordon and Kernig were negative. The superficial reflexes were uncertain because of marked muscular twitchings. These were present in the arm muscles and legs, but more marked about the lower thorax and upper abdomen.

The lung examination showed slight harshness of breath sounds, otherwise negative. There was moderate tachycardia of the heart. The abdomen was negative. Blood-pressure, 125/85.

The patient became more stuporous during the second and third day. He was almost insensible to pin pricks. The convulsive twitchings were more marked. There was a semihiccough in the convulsive twitchings about the lower thoracic and abdominal muscles and diaphragm. On the fourth day the patient was mentally more clear. He stated that he had been sick for five weeks with apparent hyperactivity and inability to sleep, together with severe pains in the arms and legs. He stated that his mind had been "foggy" and unclear, and that he had "seen double" many times. The following day he died from apparent cardiac exhaustion.

The urine examination was negative. The blood showed 10,000 white blood cells with 80 per cent polymorphonuclears, 10 per cent small lymphocytes, 2 per cent large lymphocytes, and 4 per cent transitionals. The spinal fluid was clear, it flowed freely. Globulin was present as a trace. The cells were 80 per cc, mostly small mononuclears. The spinal fluid Wassermann was negative. The temperature varied from 103° to 106°, the pulse from 120 to 150; respiration 30 to 40.

The *clinical diagnosis* was lethargic meningo-encephalitis.

Autopsy. Autopsy showed marked congestion of the meninges with increased cerebral spinal fluid. The brain itself was distinctly

red due to congestion. The lungs showed some adhesions about the left apex with a few old calcareous tubercles. The heart was normal; the aorta showed a few athermatous plaques in the lower portion. The aortic valves were somewhat sclerotic. The abdomen was negative except for a few adhesions about the gall bladder. The kidneys were negative, except for fetal lobulations. The spleen was somewhat contracted.

Microscopical Examination. This showed a few old tubercles in the lung tissue. The connective tissues of the spleen were increased. There was moderate inflammation of the kidneys.

Central Nervous System. Microscopically, the meninges of all portions examined showed small hemorrhages, which distended the membranes. These hemorrhages were most notable over the cerebellum. Aside from the widening caused by these hemorrhages, the meninges were very slightly increased in width in small patches where an infiltration by small lymphocytes and occasional plasma cells were seen. Here and there small patches of rapidly proliferating fibroblasts were seen, and in some areas granular cells were already filled with the débris from the small hemorrhages noted.

All the bloodvessels were congested. The adventitial coat as a rule showed no marked alterations, the elastic membrane was swollen. The endothelial cells were extremely swollen, and cells were frequently seen loosened at one or both ends and floating into the lumen of the vessel. Mitoses were occasionally seen in the endothelial cells. Polymorphonuclear leukocytes were seen occasionally in the lumina. No infiltration of the adventitial lymph spaces was seen in any sections of the cortex examined, but the portions of thalamus, lenticular nuclei, peduncles, pons, and medulla examined showed many small foci of plasma cells, small lymphocytes, occasional mast-cells and polyblasts around the smaller vessels, preëminently around the veins. The arteries as a rule showed no infiltration. Plasma cells were also frequently seen in the adventitial lymph spaces of the capillaries in greater numbers in the neighborhood of the above foci. An occasional polyblast, containing lipoid pigment, was seen in the adventitial lymph spaces. The lenticulars were involved to a much lesser extent than the thalami, pons and medulla, and the lesions were practically all in the globus pallidus. The substantia nigra showed more foci and of much larger size than in any other location, but the lesions were not limited to these areas. The third nerve nuclei were invaded.

The lesions in the medulla were very numerous and very diffuse, sparing, however, the olivary regions and the pyramids. Very small hemorrhages or more properly diapedeses were seen in the peduncles, medulla and basal ganglia. The locus ceruleus was especially riddled with small infiltrative foci, and foci were disseminated through all that portion of the pons dorsal to the median fillet.

The nerve tissues of the cortex, as a whole, showed severe edema, giving it a honeycombed appearance. The nerve-cell changes of the cortex varied greatly in the different layers. The small and medium-sized pyramidal cells showed severe acute alterations. The protoplasm was composed of fine granules, and the nuclei were frequently dark, discolored and irregular in form. The deeper cell layers showed much less alteration, the large motor cells were practically normal. The nerve cells in the basal ganglia, pons, medulla and peduncles on the other hand showed comparatively little alteration. A few nerve cells were destroyed by the immediate presence of an inflammatory focus, but others appeared quite normal.

Glia reactions were not very marked. Satellitosis was not increased. A certain number of ameboid cells were seen in the white substance, and in the thalamus and peduncles there were a few very small remnants of an older inflammatory process that showed as a lack of nerve cells and an excess of glia cells in the area, but none of the large actively proliferating forms of glia cells were seen.

Many amyloid bodies were seen scattered here and there in the neighborhood of the ventricles. The axicylinders in the neighborhood of the foci occasionally showed a swelling and tortuous outline, and myelin clumps and bodies were seen lying in the tissue. The nerve fibrils were unusually resistant to Bielschowsky's stain, but showed no other abnormalities.

Pathological Diagnosis. Old healed pulmonary tuberculosis; meningeal hemorrhages; acute leptomeningitis; acute proliferation and degenerative changes in cerebral bloodvessels; multiple focal encephalitic lesions in basal ganglia, pons and medulla; multiple miliary hemorrhages in basal ganglia; edema of cortex; localized acute degenerative changes in cortical nerve cells; pathological process of lethargic encephalitis.

Case VI.—R. J., laborer, aged twenty-nine years. The patient was brought to the hospital because of his semidelirious condition. The only complaint was that of diffuse bodily pains.

Present Illness. Illness began about thirty days ago with soreness in the chest, general weakness and a feeling of being tired, headache and persistent pains up to a few days before entrance. At this time the pains became more aggravated, and the patient partially uncontrollable.

Examination. This showed the patient to be a well-nourished male lying in bed partially restrained. He was untidy and apparently semiconscious. He was partially aroused, however, at a sharp command, and was fairly well oriented and answered questions fairly well.

He had a diffuse burn over the chest, back and hips, together with a macular rash over the entire body, due to the reaction of mustard

plasters, which were applied previously, because of pain. There was a diffuse muscular twitching over the entire body, but more marked over the abdomen and lower thorax. He could not lie still because of the twitching. The most marked involuntary twitchings were about the face, right shoulder and lower thoracic muscles, together with a "diaphragmatic jerk."

The pupils were slightly contracted; they reacted neither to light nor in accommodation. There was no eye-muscle involvement and the tongue protruded straight. There was no facial palsy. The biceps, triceps, umbilica, cremasteric and patellar reflexes were absent. Oppenheim, Babinski and Chaddock gave no response. Kernig was negative.

Two days later there developed a marked external rectus palsy of the right, and less marked palsy of the left eye. All deep reflexes were absent. The patient was more unclear; he could scarcely be aroused. When he was aroused he carried out commands fairly well, many times he did not do so even when spoken to in his own language. The eyes were closed for the greater part of the time. The patient developed retention of urine. He became comatose and died on the following day.

The urine examination was negative. The blood examination gave 12,000 white blood cells with 68 per cent polymorphonuclears, 12 per cent lymphocytes, 14 per cent small lymphocytes, 4 per cent large mononuclears and 2 per cent transitionals. Blood Wassermann was negative. The spinal fluid flowed freely. It was clear, with 21 small mononuclears per cc. Globulin was present as a trace. The spinal fluid Wassermann was negative.

Clinical Diagnosis. Diagnosis was meningo-encephalitis lethargica.

Autopsy of the head only was permitted. The dura was adherent over the left side of the skull cap. The meninges were much congested. The brain itself was definitely red, due to the congestion of all the small vessels. The cerebral fluid was increased. Fluid from a ventricular puncture when cultured showed a diplococcus. The brain was preserved in 10 per cent formalin for detail study.

Central Nervous System. Macroscopically, the meninges and brain were very congested, the basal bloodvessels were somewhat lessened in size and contained small sclerosed patches. The pia-arachnoid was rust colored in places. There was a small hemorrhage at the anterior edge of the left internal capsule.

Microscopically, there were small foci scattered through the dorsal part of the medulla, in which the vessel walls were infiltrated with small lymphocytes, plasma cells and polyblasts. These often contained lipoid substances. The capillaries in the thalami and basal ganglia were bordered by plasma cells. The bloodvessels as a whole showed no thickening of the adventitia, but showed swelling of the elastic and endothelial coats. Plasma cells were also seen along the capillaries in the thalami and subthalamic regions, in

the peduncles and in the gray substance of the pons. In the right caudate nucleus they were present in a few widely separated foci, and there were a few in the left globus pallidus. The vessels were all engorged and diapedeses had taken place in a few areas. A good deal of lipoid material was seen along the lymph spaces, and in one arteriole in the right anterior central region a few small lymphocytes were seen in the adventitial lymph spaces. The fatty degeneration in the smallest arterioles formed at times a complete ring, every adventitial cell being degenerated. This condition was seen especially in the caudate and lenticular nuclei and in the peduncles.

The pia-arachnoid was thin and for long stretches perfectly normal, aside from the unusual distention of the bloodvessels. In some areas there was a very moderate degree of infiltration by small lymphocytes and polyblasts, the latter much in excess of the lymphocytes and mostly filled with pigment. Rarely a plasma cell was seen.

The nerve cells in the cortex varied very much in their pathology. Many of the largest cells were normal. Many cells showed acute swelling with pale, finely granular bodies and clear swollen nuclei; others were much more seriously affected, the nuclear membrane being folded and irregular and the nucleoli flanked by small satellites. Many axonal reactions were seen. No loss in myelin sheaths was observed.

Satellitosis was considerably increased and in the Mann-Alzheimer stain many pyknotic glia cells were seen, some having a ragged protoplasm. The nerve cells in the areas invaded by foci showed remarkably little alteration, only those cells in the focal area being affected. The glia in the affected areas showed considerable proliferation, but no very large cells, most of the cells being small, with fairly normal nuclei and small protoplasmic bodies.

Pathological Diagnosis. External pachymeningitis; multiple encephalitic lesions in medulla and basal ganglia; acute reactive and proliferative changes in cerebral bloodvessels; localized acute degeneration of cortical nerve cells; localized progressive glia reactions; pathological process of lethargic encephalitis.

CASE VII.—B. A., aged twenty-one years. There was no history other than that of pains in the head of one month's standing. The patient understood but little English and was primarily of low mentality.

On examination, the patient was a well-developed male lying in bed. He was so stuporous that he could only be aroused with the greatest difficulty.

There was no ptosis of the eyelids and no definite drooping, although the lids were held closed most of the time. The pupils were smaller than normal and reacted sluggishly both to light and in accommodation. The extrinsic muscles reacted normally.

There was no facial paralysis, perhaps a slight drooping of the left corner of the mouth. The tongue protruded straight; nasal and aural cavities were negative. The deep reflexes were all negative, the skin reflexes were apparently negative. There was a marked stiffness and rigidity to the neck muscles. Flexion and extension of the thigh and leg caused pain and stiffening of the muscles.

There was a definite tachycardia of the heart. The lungs showed some impairment, especially at the left apex, with definite harshness of the breath sounds over both upper lobes. The abdomen was negative except for suprapubic fulness.

Thirty cc of spinal fluid under considerable pressure was removed. This made the patient slightly more rational and to some extent relieved the headache.

The patient had a persistent retention of urine. The amount of urine obtained by catheterization varied from 1600 to 2000 cc in the twenty-four hour period.

On the fourth day in the hospital, 25 cc of spinal fluid was again removed, with slight improvement in the patient's condition.

On the seventh day of observation there was a definite change in the *neurological examination*. The patient responded somewhat better to commands. In the pupils no definite reaction could be observed either to light or in accommodation. The pupils were about equal, but somewhat smaller than normal. The right lid had a definite ptosis of small degree. A definite external rectus palsy on both sides was present. The facial movements were normal. The biceps and triceps reflexes were present but diminished. The patellar and Achilles were absent for the first time. The Oppenheim, Gordon, Babinski and Chaddock were normal.

Retention of urine persisted together with the increased volume. On the ninth day partial drainage of 45 cc of the spinal fluid was done with but slight improvement in the patient's condition. He died on the tenth day.

The urine showed a specific gravity of 1016, some albumin, a few pus and red blood cells in the sediment.

The blood report gave 3,900,000 red blood cells; 9000 white blood cells with 65 per cent hemoglobin; polymorphonuclears were 86 per cent; eosinophiles, 1 per cent; large lymphocytes, 1 per cent; small lymphocytes, 11 per cent; large mononuclears, 1 per cent. The blood Wassermann was negative.

The spinal fluid was clear on three occasions and showed 400, 450 and 230 cells per c.mm. The pressure and amount was always increased. The globulin was always heavy. The Wassermann on all occasions was negative. The cells were mixed large and small mononuclears. The large cells in many instances were definitely ameboid in character.

The temperature varied from 100° to 104°, the pulse gradually ascended from 70 to 140, respiration from 20 to 30.

An unsuccessful attempt was made to demonstrate tubercle bacilli in the spinal fluid.

Autopsy. This showed thickening of the meninges. There were no definite tubercles. There was a marked venous congestion of the pia. The cerebrospinal fluid was much increased, although fairly complete drainage was instituted the day previous. The brain gave the general appearance of redness from the injection of the small vessels. In the apices and the axillar region of the left lung there were fairly numerous, old, healed, miliary tuberculous nodules. The heart and aorta were quite normal. The liver was somewhat enlarged and congested. The spleen was grossly normal. Both kidneys were definitely of the "horseshoe" type. They were slightly enlarged, somewhat granular when stripped, with marked fetal lobulations. The gastrointestinal tract was normal. The *microscopical examination* showed the lungs to be congested and numerous miliary tubercles. The heart was negative except for cloudy swelling; pancreas was normal. The liver showed congestion, many tubercles were present in the spleen. The kidneys were congested together with dilatation of tubules and sclerosis of some of the glomeruli.

Central Nervous System. At the *autopsy*, the brain was white and showed extreme congestion of the meningeal vessels. The pia-arachnoid was opaque. There was moderate internal hydrocephalus.

Microscopically there were several small hemorrhages scattered through the pia-arachnoid. All portions of the pia-arachnoid that were studied showed a severe type of tubercular meningitis with many tubercle bacilli. The posterior velum, the choroid plexus of the fourth ventricle and the subependymal tissue of the basal ganglion showed vessels densely infiltrated by small lymphocytes, plasma cells and small and large phagocytes. The villi of the choroid plexus in the region of the inflammatory reaction showed partial to complete loss of the secretory cells. The ependyma was comcompletely broken through by small glial proliferations.

The meningitis was very diffuse in all areas, but much more severe over the medulla, pons and peduncles. In the denser portions many polynuclear leukocytes were present. No giant-cells were observed. The vessels passing in from the pia of the medulla and in the raphé were infiltrated for considerable distance with small lymphocytes, but no plasma-cell infiltration of the capsule was seen, and mast-cells were absent. The vessels passing in from the region of the pons and peduncles were similarly infiltrated. There were foci, in which this infiltration was present, in the substantia nigra, in the third nerve nuclei, in the internal geniculate bodies and in the corpora quadrigemina.

Inflammatory foci were seen scattered through the thalami and caudates and to much less extent in the lenticular nuclei. The nerve cells in all portions of the central nervous system showed

lack of chromatin and a very few cells showed axonal reactions or stained a dark color. The glia in the cortex was negative except for some porliferative and regressive phenomena in the molecular layer. The subependymal glia was enormously increased, especially where infiltrated vessels were seen, and there was very marked glia proliferation on the margins of the medulla, pons and peduncles. The bloodvessels showed no thickening of their adventitial or elastic coats, but the endothelia was swollen, proliferating and frequently floating loosely in the lumen of the vessels.

Pathological Diagnosis. Chronic pulmonary tuberculosis; tuberculosis of the spleen; multiple hemorrhage in the pia-arachnoid; tubercular leptomeningitis.

Case VIII.—A. B., female, aged twenty-three years. The patient stated that she first became ill about one month previous to our examination with severe pains in the head (frontal and occipital regions). Headaches and pains occurred periodically during the following weeks. At one time there was a severe pain in the foot for several days; later on similar pains were felt in the shoulder and arms. These pains recurred in various muscles of the body for about four weeks. The patient said she could not sleep at night more especially for the past week. She had been "sleepy all the time." For about one week "double vision" was present. At the time of examination she thought she saw her friends at the bedside at intervals and called to them and thought they touched her. Photophobia had been marked for about one week with definite drowsy feeling of the eyelids for three weeks past. At the same time there was a twitching of the muscles of the arms, legs, lower thorax and abdomen.

On *examination* the patient did not appear very sick although she picked at the bedclothes and closed the eyes as in a mild sleep, especially when her attention was not sharply stimulated. Apparently she was rational but mentally retarded. Her headache was located by placing the finger on the frontal and occipital regions. There was a definite drooping of the eyelids without definite ptosis. The right eye did not turn so far to the right as the left eye turned to the left. The pupils reacted sluggishly both to light and in accommodation. There was spasmodic twitching of the upper recti, midgastric, and the ninth, tenth and eleventh intercostal muscles. The biceps, triceps, umbilical, patellar and Achilles reflexes were normal. Plantar stimulation caused no response; no Kernig. There was a slight stiffness in the neck muscles when the head and neck rotated.

The lungs were negative. The heart-rate was increased. The abdomen was negative to palpation.

The patient gradually became weaker, respiration and pulse both became gradually accelerated. At the end of the first week

in the hospital there had occurred a definite progressive change in the *neurological examination*. At this time the pupils did not respond to light or accommodation tests. Both sides showed extra-ocular muscle palsies. The eyelids drooped, but were not paralyzed. There was a definite weakness of the left side of the face but the tongue was protruded straight.

The biceps and triceps reflexes, while present, were distinctly diminished on the right side. The umbilical and patellar reflexes were absent. The Babinski, Oppenheim and Gordon reflexes were normal on the right with no response on the left. Flexion of the head caused pain in the back of the head. There was a definite weakness of the throat muscles on swallowing and coughing. There was a spasmodic movement of both shoulder muscles, together with an irregular spasmodic movement about the diaphragm, not dependent on respiratory movements, and irregular twitching of the lower thorax was present on both sides. The chest examination was negative. Four days later the patient voided involuntarily. At this time the patient's heart became apparently much weaker. The *neurological examination* was about the same as before. Respirations were increased together with a "grunt." There was a general harshness of the breath sounds with diffuse moisture at the bases. The heart-rate was much increased and decidedly weaker, producing a thready pulse. A vesicular rash of the neck, head and chest was present, due to irritation and persistent and marked perspiration.

The urine was negative on repeated occasions. The blood showed 4,400,000 red blood cells; 13,250 white blood cells; 78 per cent hemoglobin; polymorphonuclears, 70 per cent; large lymphocytes, 10 per cent; small lymphocytes, 12 per cent; large mononuclears, 6 per cent; transitionals, 2 per cent. Blood Wassermann was negative. The spinal fluid was clear, under pressure, with a faint trace of globulin, 30 cells per c.mm. The Wassermann was negative.

Drainage of the spinal canal on two occasions relieved the headache temporarily, but this was only a transitory result. Patient died on the thirteenth day in the hospital from general, but chiefly cardiac exhaustion.

Clinical Diagnosis. Lethargic meningo-encephalitis.

Autopsy. The dura was found markedly adherent. The meninges were much congested. The vessels were dilated, but no nodules were present. The pia was distinctly cloudy, more dense than normal, and slightly elevated from the increased cerebrospinal fluid. The meningeal inflammation was probably greater at the base than over the vertex. The accessory sinuses were negative.

The lungs showed hypostatic congestion, with a small area of bronchial pneumonia. The heart was negative. The liver was negative. The kidneys showed fetal lobulation, otherwise negative. The ovaries, tubes, uterus, pancreas and spleen were normal.

Microscopical Examination. This was practically negative for other than slightly cloudy swelling, congestion and edema of all the organs.

CENTRAL NERVOUS SYSTEM. *Autopsy* showed a very edematous brain with extreme congestion of the meningeal vessels. The pia-arachnoid was not thickened or opaque, but showed many small hemorrhagic areas on the frontal and parietal lobes. The divisions of many sulci were agenetic in type.

Microscopically, the pia-arachnoid showed many small hemorrhages. Here and there were small areas of acute fibroblastic proliferation with a few small lymphocytes, plasma cells and polyblasts.

The bloodvessels were congested and frequently the whole lumen was packed with polynuclear leukocytes. The adventitial coats showed no alteration. The elastic membrane showed slight splitting. The intima was sometimes congested with many of its cells small and shrunken.

In the basal ganglia, peduncles, pons and medulla many vessels showed dense infiltration of the adventitial lymph spaces by small lymphocytes, plasma cells and polyblasts. While the veins were more frequently involved than the arteries, an occasional artery was seen with a moderate amount of infiltration. A very marked infiltration of the capillaries by plasma cells was also seen. These foci were scattered irregularly through the caudates and lenticulars. Foci were numerous in the third nerve nuclei, the substantia nigra and the anterior corpora quadrigemina. The foci in the medulla were mostly very small and lay near the ventricle. Several foci of old inflammatory lesions were seen in the medulla, the caudates, thalami and peduncles. In these areas the nervous tissues had disappeared and the space was apparently entirely occupied by glia fibers and cells. There was no marked glia reaction around the recent inflammatory foci. The glia in the cortex was somewhat increased in the molecular layer and many large spider cells were seen in the white matter along the border of the polymorphous cell layer.

The nerve cells of the cortex were unusually pale, but retained their form. The nuclei showed a breaking up of the nuclear substance with displacement of the pigment to the border of the nucleus. Sometimes this granular appearance of the nuclear pigment was so marked that it gave a small pyramid cell the appearance of a glia cell. In other cells the nucleolus was still present, but two or three satellite-like bodies were near it. The nerve fibrils showed no alteration in Bielschowsky's stain.

The nerve cells of the basal ganglia, midbrain, etc., showed very little alteration, except when directly involved.

Pathological Diagnosis. External pachymeningitis; hypostatic congestion of lungs; bronchopneumonia; cloudy swelling; edema and congestion of all organs; edema of brain; hemorrhages of pia-

arachnoid; focal proliferative changes in pia-arachnoid multiple; focal encephalitic lesions in basal ganlia, peduncles and medulla; diffuse degenerative changes in cortical nerve cells; pathological process of lethargic encephalitis.

CASE IX.—R. C., aged sixteen years. The patient was admitted in an excited delirious state. No definite history was obtainable except that a friend said she had complained of a sore throat a few days previous.

The patient on examination was actively agitated. There was no coöperation or response to questions. She was physically well-developed and negative on general examination, except for an increased heart-rate without other definite auscultatory findings.

Neurologically, the knee-jerks were questionably absent. Accurate data concerning the reflexes was impossible to obtain, due to the very generalized choreiform movements of the entire body, but more especially of the arms and face. It was necessary to restrain the patient with a sheet.

A small infiltration about the left elbow developed, from which a streptococcic pus was obtained.

The temperature (rectal) was constantly elevated, ranging from 102° to 104°. The heart-rate was regular and varied from 120 to 160. It gradually increased as the disease progressed.

The white blood cell count was 14,000; polymorphonuclears, 78 per cent; large lymphocytes, 9 per cent; small lymphocytes, 8 per cent; large mononuclears, 3 per cent; transitionals, 1 per cent. The urine (catheterized) was negative. The lumbar puncture was done, of necessity, under ether anesthesia. The fluid was clear, cells 3 per c.mm. The Wassermann was negative both on blood and spinal fluid.

Clinical diagnosis was chorea insaniens of acute streptococcic origin. The possibility of an acute form of lethargic encephalitis of the choreiform type, however, was suggested by the attending neurologist. The active muscular movements were considered to be of central origin, due to stimulation by irritation.

The patient died on the seventh day in the hospital, chiefly from cardiac exhaustion.

Autopsy (two-hour postmortem). Head: The dura was quite firmly adherent over the entire skull cap. The brain was markedly congested, grossly very red, with marked increase of fluid beneath the pia in the sulci. A right anterior ventricular puncture gave a slightly cloudy fluid, from which short-chained streptococci were cultivated. The accessory sinuses were negative. The brain was suspended in 10 per cent formalin for detailed study.

The lungs showed moderate congestion. The heart was but slightly enlarged. There were a number of fragile vegetations along the margin of the mitral valves. Cultures gave a short chained

streptococcus. The spleen was quite soft and congested. The organs otherwise were grossly negative. *Microscopically*, the heart valves showed a small round-celled infiltration with some degeneration and necrosis. The liver showed edema, congestion and the kidneys slight cloudy swelling.

At *autopsy* the brain was noted as very bright red, with many small submeningeal hemorrhages.

Microscopically, the most prominent element in the picture was severe edema of all the tissues, engorgement of all bloodvessels and hemorrhages. These were severe in and under the pia-arachnoid and of moderate degree in all other locations. In addition a small number of infiltrative foci of very small extent were seen. These never formed a real sheath around any vessel, and affected a small area only. The infiltrative cells were lymphocytes with occasional polyblasts. Many vessels were filled with white blood cells. The areas of predilection of the foci were: medulla, midbrain and thalami. Although the infiltrative foci were very small in extent and number, their seat was that usual in lethargic encephalitis and with the multiple hemorrhages, general edema, moderate nerve-cell degeneration and moderate glial reaction, formed a fairly characteristic picture of that disease.

Case X.—A. J. The patient was a large adipose Lithuanian woman of approximately twenty-five years. She neither understood nor spoke English. She was brought to the hospital from a rooming-house by the police ambulance, because of a delirious mania said to have been precipitated by the desertion of a fellow countryman paramour.

Under observation she was continually excited, untidy, with no regard for her personal appearance. She sang incoherently and uttered baby-like calls. It was necessary to restrain her, and when so restrained in bed, she kept up continuous oscillatory, masturbatory movements, with a succession of short excitement periods.

Because of the excitement and resistance the physical examinations were never complete. On entrance there was no fever, axillary or rectal. The heart and lungs were apparently normal. There were unquestionable changes in the light reactions of the eyes. The reflexes could not be accurately determined.

Catheterized urine examination was quite negative.

The blood Wassermann was ++++ positive.

Under ether anesthesia a lumbar puncture was made. The fluid flowed freely. It was clear and contained 40 white mononuclear cells per c.mm. The globulin was ++++. The Wassermann was positive with 0.8 cc and the mastic was 444432100.

Mercury intramuscularly, together with arsphenamine intravenously, and spinal drainage under anesthesia with the reinjection

of autogenous serum, did not apparently affect the course of her disease.

During the third week in the hospital the patient developed a slight fever and coincidently a purulent discharge from the right ear. As the patient did not speak English at all and Lithuanian only unintelligently and made no demonstration of having pain, middle-ear infection was not suspected. The left ear, on examination showed a bulging membrane.

With the coincidence of an acute infection and the exhaustion asthenia the heart quite suddenly became irregular and rapid. The temperature was 100° axillary. There was no definite clinical evidence of meningeal inflammation before death.

At *autopsy* the dura was slightly more adherent than normal over the vertex and at the base. The cerebrospinal fluid was increased. The pia was injected. There was no evidence of pus. The convolutions showed no gross atrophies.

The mastoid cells when opened were both filled with a seropurulent material. The accessory respiratory sinuses were negative.

Except for increase in body fat, some atheromatous plaques in the aorta and renal congestion, the general autopsy findings were negative.

Central Nervous System. The *autopsy* showed marked congestion of vessels of the meninges, the pia-arachnoid thickened and opaque, agenetic sulci, and granular ependymitis of the fourth and lateral ventricles.

Microscopically, wherever the pia-arachnoid was present, a more or less intense meningitis was seen. The fibroblastic elements showed some proliferation. There were large numbers of plasma cells, mast-cells, small lymphocytes and some polyblasts lying in the meningeal tissues.

The bloodvessels had practically normal coats, but the adventitial lymph spaces were much distended and often packed with plasma cells and lymphocytes. The capillaries in all parts of the cortex examined were infiltrated more or less by plasma cells. This infiltration was much more marked in the frontal than in other regions. Considerable lipoid pigment was seen along the vessels. The bloodvessels of the raphé in the medulla, at the level of the twelfth nerve nuclei, showed some round-celled infiltration.

In the pons several densely-infiltrated vessels were seen in the fifth nerve nuclei, and in the midbrain plasma-celled infiltration of the capillaries was general. Infiltrated vessels were also seen in the third nerve nuclei, in the red nuclei and the substantia nigra. The ependyma of the aqueduct at this level was irregularly but markedly proliferated and showed infiltration by plasma cells and lymphocytes. Plasma-celled infiltration of the capillaries was not so general at this level as in the pons.

Infiltrated vessels were seen scattered through the thalami and

the caudate nuclei, and in the caudates in particular there was very general plasma-celled infiltration of the capillaries, much more than in the anterior central and calcarine areas.

There was no loss of nerve cells and the individual cells showed remarkably little severe change. In general, they were very pale, the chromatin which remained being in fine granules. The nuclear membranes were folded and the nucleoli were frequently broken up into small fragments, and when a distinct nucleolus was still present, as in the majority of cells, there were two or three small accessory bodies. Fatty degeneration was slightly in excess of the normal. No alterations were seen in Bielschowsky's fibril stain.

The fibrous glia was much increased, especially in the molecular and polymorphous layers, and large numbers of glia cells in all areas showed regressive alterations, the nuclei being small, pyknotic and irregular in form. By the Alzheimer-Mann stain many spider cells of unusual size were seen. Rod cells were present in large numbers, and many of these presented transitional forms, some bent at an acute angle, others showing a branching of the protoplasm at one end, etc. Ameboid cells were not seen.

Pathological Diagnosis. Acute purulent mastoiditis; early cardiovascular syphilis; subacute leptomeningitis; chronic meningoencephalitis; histopathological reactions of general paresis.

CASE XI.—A. W. The patient was a white male, aged twenty-one years. No definite history was obtained, as he was taken from a room in a semicomatose condition by the police. It was said that there were gas fumes about his room.

On examination, he was found to have a temperature of 102°; pulse of 140, and respiration, 36. The heart, lungs and abdomen were quite negative. There was a purulent mucus discharge in the posterior pharynx. The *neurological examination* showed all superficial reflexes to be absent. Positive Babinski on the left; a marked reflex of defense on the right, with a questionable Babinski. There was no paralysis of the extremities. Patellar reflexes were slightly increased. Kernig was doubtful.

The pupils were small and slightly irregular in outline, but the direct and consensual light reflex was present. It was impossible to test accommodation. The eye grounds were negative except for some increase in redness about the nerve head. There was no involvement of the eyelids or extrinsic muscles in so far as examination could be made.

The ears both showed retraction of the tympanic membrane.

The left membrane apparently had been perforated at some time previously. There was no discharge and no evident mastoid involvement.

Anteroposterior stereoroentgen-ray films and lateral films showed the outline of all the sinuses. They all apparently contained air.

The sphenoid especially showed a definitely thickened lining membrane. They did not suggest a sinus empyemia as was noted later. The patient became restless and moaned most of the time. The temperature gradually increased to 109° F., before death on the third day.

The catheterized urine examination was negative. The blood count showed white blood cells 17,950; polynuclears, 85 per cent; large lymphcytes, 4 per cent; small lymphocytes, 5 per cent; large mononuclears, 2 per cent; transitionals, 4 per cent.

The blood Wassermann was negative. The spinal fluid was clear, flowed freely, cells and globulin were not increased. Wassermann and mastic reactions were normal.

Autopsy. Autopsy showed that the dura was quite firmly adherent over the vertex and base of the skull. The meninges were markedly congested. All the small vessels over the convolutions were filled with bright blood. All the veins were engorged with dark blood.

When the membranes were removed from the bone over the mastoid cells a dark discoloration of the bone was noted. There was no marked local meningeal reaction in these areas. The inner table of bone in these parts was easily removed with the point of a knife, opening the mastoid cells. They were voluminous on both sides. The uppermost cells on both sides were filled with a thin reddish fluid. The venous sinuses were not thrombosed.

The sphenoid and both ethmoids were filled with a foul, thick pus. The lining membranes of the cells were much thickened, and darkly colored, due to changed blood. There was no gross evidence of any direct path of infection between the sphenoid, ethmoids and meninges.

The right lung showed some old healed tubercles at the apex. Except for congestion, the heart, liver, kidneys, pancreas, spleen, stomach and intestines were negative.

At *autopsy* the brain appeared markedly congested, the small arteries over the convolutions being filled with bright red blood and the veins engorged by dark blood. The basal bloodvessels were rather small and showed some slight thickened patches.

The pia-arachnoid was rust-stained over the frontal poles. Small punctate softenings were seen in both globi pallidi.

The left hemisphere of the cerebellum was considerably smaller than the right.

Microscopically, the pia-arachnoid showed no increase in width in general, but in many areas, notably in the cerebellum and right Ammon's horn, hemorrhage had taken place, spreading the tissues. In the Ammon's horn the hemorrhage had already begun to organize, showing proliferating fibroblasts, also large numbers of polyblasts were present. The adjacent edges of the cortex had been invaded by the hemorrhages in several places.

All bloodvessels were excessively engorged with blood to such an extent that the cortical architecture was much disarranged. The adventitial coats showed no alteration but the elastic was slightly swollen. The endothelial cells of the vessels showed very active proliferation, many mitoses being seen and the cells were excessively swollen. Diapedesis was constant in all sections, but larger masses of blood, real hemorrhages, were also seen to a slight extent in the cortex, but more marked in the medulla and the globus pallidus of each side. In the medulla several vessels were seen in which the adventitial lymph spaces were packed with small lymphocytes and polyblasts, but no plasma cells were observed.

In both the right and left globus pallidus vessels were seen with a moderate amount of infiltration by small lymphocytes and mast-cells. Most noticeable of all was the very active proliferation of adventital tissue around the vessels where constant mitoses were seen in great numbers. Several foci were seen in both nuclei where a vessel was surrounded by large masses of polynuclear leukocytes invading the tissue in all directions. Many degenerated foci were seen, some recent, showing hemorrhage with the beginning of phagocytosis and others older, some almost devoid of all cellular elements, others were packed with small phagocytes containing fat (granular cells) and still others where granular cells were present, but glia and connective tissue predominated. The left lenticular showed the same conditions as seen in the pallidi. Granular cells were scattered throughout all portions of the sections examined, both near and at a distance from vessels. These were frequently seen dividing both mitotically and amitotically and were probably both mesodermic and gliogenous in origin.

The nerve cells of the cortex were practically all in the first stages of dissolution of the protoplasm. Their bodies were finely granular and pale. The nucleoli showed invariably a splitting up of their substance into three or more bodies, frequently arranged in a row or in star form (a process considered by the Spanish school to be an attempt at proliferation by mitoses). There was some excess of satellitosis in the cortex, but it was not at all marked. There was also some proliferation of glia cells where hemorrhage had invaded the cortical margin and especially when organization had already begun in the hemorrhage. This condition was specially notable in the cerebellum.

Pathological Diagnosis. Acute purulent mastoiditis; old healed tubercles of lung; congestion of body organs; cerebral congestion; localized meningeal hemorrhages; acute proliferative changes in cerebral vessels; multiple cortical hemorrhages; multiple focal encephalitic lesions, chiefly in the basal ganglia; severe degenerative changes in cortical nerve cells; histopathological process of lethargic encephalitis.

DIFFERENTIAL CLINICAL DIAGNOSIS.

In the group of cases we have presented the following disease entities must be considered: Meningo-encephalitis lethargica, tuberculosis, meningo-encephalitis, syphilis of the central nervous system, tetanus, streptococcic meningo-encephalitis and chorea insaniens. In addition to these conditions acute cerebral manifestations are seen in botulismus, cerebral tumor, typhoid fever, acute delirium in hysteria, trypanosomiasis, uremia, anterior poliomyelitis, and epidemic cerebrospinal meningitis.

Botulismus usually is associated with a definite history of food poisoning, with severe acute gastrointestinal symptoms together with some cerebrobulbar symptoms. The infective agent may be discovered and the clinical course of the disease is usually afebrile.

Typhoid is usually eliminated by the physical and laboratory findings common in typhoid fever.

Cerebral tumor has been misjudged ofttimes during the last pandemic, especially in the rare case where the cardinal symptoms of headache and intracranial pressure as shown in the fundus were absent. A careful anamnesis, neurological examination, and, as a rule, negative laboratory findings, together with a few days' observation, will usually suffice to make differentiation possible.

Acute delirium usually gives only the delirium, unassociated with fever, abnormal laboratory findings, or neurological disturbances.

Chorea insaniens may present difficult problems, as witnessed in one of our patients. With the evidence of an acute streptococcic infection or the common lesions produced by such an infection, as endocarditis, the diagnosis is suggested. Numerous observations of choreiform movements have been recorded in patients diagnosed as lethargic encephalitis. The question is justly raised in consideration of our case, whether one should consider that there is a choreiform type of encephalitis lethargica. The movements produced by cerebral irritation or by stimulation are not necessarily due to one type of infection. Further, the cases of this type present a most difficult problem, for in our patient who had a violent agitation, and the postmortem finding of acute friable vegetations on the mitral valves, Dr. Gurd has found so many histopathological changes that the brain specimen cannot be classified separately from the brains of characteristic encephalitis lethargica.

Hysteria is usually apyrexic. We must rely largely on the stigmata: sensory disorders, contracted visual fields, anesthesias, and the unchanged reflexes and negative laboratory examinations.

Trypanosomiasis has presented interesting similarity in the pathological brain findings, but fortunately we are seldom called upon to make a clinical differentiation.

Uremia will usually be excluded by: (1) Urine examination; (2) blood-pressure; (3) blood chemistry; (4) increased incoagulable

nitrogen in the spinal fluid as shown by direct Nesslerization, and (5) the absence of any definite evidence of infection as shown by fever. In one of our patients typical encephalitis lethargica was complicated by a chronic nephritis with moderate hypertension.

Epidemic cerebrospinal meningitis gives a cloudy spinal fluid, containing large numbers of pus cells with intracellular diplococci. Further, as a rule, the stormy onset with fever and acute severe meningospinal symptoms, as head pains, stiff neck, opisthotonus, rigidity and Kernig's signs, together with the eye and neurological findings are sufficient to obviate difficulty in the differential diagnosis.

Anterior poliomyelitis, when the meningo-encephalitic complex is prominent, presents difficulties which are confusing, whereas in the presence of selective paralysis of the extremities the diagnosis would be more evident. The stormy onset, with marked fever, ofttimes vomiting, severe headaches, meningeal symptoms, associated with early evidence of true motor paralysis, is more characteristic of this condition. The spinal fluid examination will differentiate this condition from meningococcus infection and acute syphilis.

Our cases deal more specifically with tetanus, tuberculosis, syphilis and acute encephalitis, both of the lethargic and streptococcic types.

Tetanus under the conditions of one of our patients did not present the classical syndrome. Except for the tetanic contraction of the masseter muscles, the case might clinically have belonged to other encephalitic diseases. The serological examination of the spinal fluid, together with the low globulin content is against syphilis; on the other hand the white cell count of both the spinal fluid and blood is in favor either of tetanus or tuberculosis, however, in our cases tuberculosis always gave a very marked globulin reaction. Our patient probably had a cephalic type of tetanus, but without the evidence of a portal of entry we feel that, in the absence of the finding of tubercle bacilli in the spinal fluid, a positive differential diagnosis could not be made between tuberculosis and tetanus without the *micropathological study* of the brain. The marked pleocytosis in the spinal fluid is a definite argument against encephalitis lethargica. Further, the complete lack of involvement of the nerves of the eyes is most unusual in lethargic meningo-encephalitis.

Tuberculous meningo-encephalitis may present a mixed complex, varying on the extent and locating of the brain lesions. That the disease is a true encephalitis, especially in adults, is evidenced by the fact of the marked pathological reaction and the finding of the bacilli within the encephalon. As a rule, the meningeal involvement is more marked than is seen in encephalitis lethargica. This probably accounts for the greater severity of the headache. Tuberculosis, as a rule, gives bizarre colloidal reactions, whereas syphilis gives definite reactions together with specific complement-fixation.

Streptococcic encephalitis may occur and show minimal meningeal involvement. This accounts for the negative spinal fluid as found in Cases IX and XI, although the brain sections showed extensive changes. An infected wound, a streptococcic sore throat, or an infected accessory or mastoid sinus would suggest this type of encephalitis.

Acute syphilis is polymorphous in its manifestations and must, as a rule, be diagnosed by the much increased cell count of the spinal fluid, marked globulin increase, colloidal reactions and the specific complement-fixation tests.

Lethargic meningo-encephalitis, to us, in spite of the many so-called forms described in the recent voluminous literature, presents a fairly definite clinical complex. It has ofttimes been said that the condition must be diagnosed by a *process of elimination*, yet a considerably confusion is existing because the disease presents many phases, and some of the cases reported as such have not had the proper *laboratory* and *clincal tests*, and most of all, the *histopathological* confirmation. The basis of classification of clinical manifestations is confusing because many signs may be presented depending upon the location of the pathological reaction. However, when the whole clinical picture is obtained, there is, as a rule, a fairly constant clinical entity. The combination of *fatigue, lethargy, headache, giddiness, visual disturbances* of which *diplopia* is most common, together with *fever, progressive weakness, mental dulness radicular pains,* and definite *neurological findings* is not usually seen in other conditions. These taken together with *slight increase* in the *white blood cells*, and *spinal fluid examination* give a definite picture. In our experience the spinal fluid has always been slightly changed. The cells have varied from 20 to 80. The globulin has always been present in a trace and there have been slight colloidal changes. Two factors influence the cell count in this condition, namely, the age of the fluid, and the apparent stage of the disease. In a number of cases where spinal drainage was done for therapeutic reasons, the cell count progressively decreased. The spinal fluid has an increased volume as shown by the frequently repeated drainage and also at postmortem.

We do not wish to present a lengthy résumé of the various findings in encephalitis lethargica because recent literature contains many excellent reviews. The clinical diagnosis must of necessity be made with most assurance when the composite picture is presented of history, physical examination, blood and spinal fluid, and urine examination. In our experience the spinal fluid showed the most consistent changes. Unfortunately the amount of glucose was not determined in our cases. Dopter and Netter, as quoted by Benard[1] consider that "l'hyperglycorachie" is a very important finding in encephalitis lethargica: Benard says, however, that increases are found in diabetes, uremia, bronchial pneumonia, Malta fever, rabies,

pertussis and cerebral tumor, and the increase in acute encephalitis should be considered merely as additional evidence. It probably indicates that the "centre de la glycogenese est touché." This examination is of importance in the differentiation of the lethargic types from tuberculosis. We have found, as Netter states,[2] that there is a tendency for the pleocytosis of encephalitis lethargica to change as the disease progresses. The cell count is usually higher in the earlier stages of the disease. In reviewing the reported cases and in studying the patients we have seen, it seems to us that the spinal fluid changes are quite constant in encephalitis lethargica, and further that a differential diagnosis is not warranted without this laboratory data. In the differentiation from tuberculosis, Netter[2] has stated the lymphocytosis is not infrequent in encephalitis lethargica, but is less than occurs in tubercular meningitis.

The Wassermann fixation and the colloidal chemical reactions serve best to differentiate tuberculosis from the various syphilitic diseases. Leukocytosis is quite common in tuberculous meningoencephalitis, rare in syphilis and very moderate in encephalitis lethargica.

There has been considerable discussion concerning the serological reactions in encephalitis lethargica, especially the colloidal reactions. Recently a patient, who had a well-developed Parkinson syndrome, was studied in consultation with Dr. Charles McVey, by one of us (Gilbert). The patient had residuals of eye muscle involvement, especially of the pupil, with a history of what was undoubtedly an acute encephalitis of a year past. The blood Wassermann showed a very slight complement-fixation, while the spinal fluid showed an increase of a few cells, a slight trace of globulin (Pandy), a three plus complement-fixation with human-heart-cholesterinized antigen, using 0.8 cc of spinal fluid and a colloidal-gold reaction of 2455431000 and mastic of 121000000. Subsequent antiluetic treatment had no effect on the patient's condition. Leavitt[3] reported a case of paralysis agitans type of lethargic encephalitis that showed a positive Wassermann reaction on the spinal fluid, a cell count of 22, a positive globulin reaction and a colloidal gold curve of 3455432110. The blood Wassermann was negative. The patient had severe bodily pains, incontinence of urine and feces. The pain was followed in three weeks by tremors and speech changes. The condition of the patient became progressively worse under antiluetic treatment.

The serological changes which we have mentioned in the two preceding cases are of marked interest in relationship to some of the specific pathological changes noted by Dr. Gurd in the brains of patients dying of encephalitis lethargica. It has been observed that there is constantly a marked fatty change in the endothelial cells about the foci as seen in the brain sections. In view of the fact that these changes are most marked about the small veins and in the lumen of the same, it would be logical to suppose that in the later

stages of this condition there may be definite lipoidal changes which might reasonably be supposed to affect the serological reactions of the spinal fluid and possibly also that of the blood.

CHART I.—BLOOD EXAMINATION.

Case.	White blood cells.	Polymorphonuclears.	Eosinophiles.	Basophiles.	Large leukocytes.	Small leukocytes.	Large mononuclears.	Transitionals.	Wassermann.	Blood nitrogen, gm. per 100 cc.
I	13,000	73	0	0	10	7	6	4	Neg.	
II	10,000	75	0	0	5	11	5	4	Neg.	0.042
III	16,500	..	..	..	..	..	..	..	Neg.	
IV	15,450	89	0	0	4	2	5	0	++++	
V	10,000	80	0	0	2	10	4	4	Neg.	
VI	12,000	68	0	0	12	14	4	2	Neg.	
VII	9,000	86	1	0	1	11	1	0	Neg.	
VIII	13,250	70	0	0	10	12	6	2	Neg.	
IX	16,000	78	0	1	9	8	3	1	Neg.	
X	8,000	..	..	..	..	..	..	..	++++	
	31,000	85	0	0	5	6	2	2	..	*
XI	17,950	85	0	0	4	5	2	4	Neg.	

* Coincident with otitis media.

CHART II.—SPINAL FLUID EXAMINATION.

Case.	Character.	Pressure.	Cells.	Globulin.	Wassermann.	Mastic.	Clinical diagnosis.
I	Clear	+	260	++++	+?	221100	Tuberculous meningo-encephalitis.
	Clear	+	200	++++	+++	211000	
II	Clear	+	50	Trace	Neg.	110000	Lethargic meningo-encephalitis.
	Clear	+	20	++	Neg.		
III	Clear	1	300	+	Neg.	110000	Tetanus or tuberculous meningitis.
IV	Clear	+	150	++++	Neg.	111000	Tuberculous meningo-encephalitis.
V	Clear	+	80	Trace	Neg.	111100	Lethargic meningo-encephalitis.
VI	Clear	+	21	Trace	Neg.	110000	Lethargic meningo-encephalitis.
VII	Clear	++	400	++++	Neg.	211110	Tuberculous meningitis.
	Clear	++	450	++++	Neg.		
	Clear	++	250	++++	Neg.		
VIII	Clear	+	30	Trace	Neg.	111000	Lethargic meningo-encephalitis.
IX	Clear	1	3	0	Neg.	000000	Streptococcus encephalitis.
X	Clear	+	40	++++	++++	444432100	Acute paresis; otitis media.
XI	Clear	0	3	0	0	0	Streptococcus encephalitis; lethargic meningo-encephalitis.

The Histopathological Résumé. The *pathology* of the cerebrospinal nervous system so far as studied in the eleven cases here presented falls readily into several distinct groups.

In Cases I, IV and VII, a typical picture of tubercular meningo-encephalitis is offered. Although the cases vary in some details the following phenomena are common to all: Macroscopically severe leptomeningitis, internal hydrocephalus and cystic choroid plexes.

Microscopically tubercle bacilli were found in greater or lesser numbers in each case, the meningitis was characterized by the presence of lymphocytes, plasma cells, giant-cells, polyblastic granular cells, but especially by the presence of large numbers of large pale giant phagocytes. The inflammatory process had invaded the choroid plexus to a greater or lesser extent in each case and also the ependyma of the ventricles. Case VII, in which the internal hydrocephalus was less marked than in the other two cases also showed less involvement of the ependyma by the inflammatory process.

Many bloodvessels showed swelling and loosening of the endothelial lining which was frequently seen floating in the vessel lumen attached only at one point.

In each case considerable involvement of the nervous tissues had taken place by the extension of the inflammatory infiltration along the course of the vessels entering from the pia. This involvement was always more marked at the base of the brain and in addition small inflammatory foci were seen scattered irregularly in the medulla, pons, peduncles and basal ganglia, but in Cases I and IV particularly noted in the nuclei of the third nerves.

The nerve cells were more or less injured in accordance with their proximity or remoteness from the inflammatory process.

Glia reaction was very marked in all areas where the meningitis was present and varied with the severity of the meningitis process and the presence of the inflammatory foci.

Cases II, V, VI, VIII and IX present the more or less typical findings of acute (to some extent) chronic meningo-encephalitis occurring with the syndrome termed lethargic encephalitis.

All the nervous structures showed extreme edema both macro- and microscopically. In most of the cases the brains were of a cherry-red on autopsy.

The meningitis was always very slight and only seen in patches. Hemorrhage in the meninges was present, and in some of the cases but not invariably, very small hemorrhages and diapedesis, mostly in the basal ganglia, pons, peduncles and medulla. The meningitis consisted of an infiltration of very slight density by lymphocytes and occasional plasma cells.

No inflammatory foci were seen in the cortex. Inflammatory foci were observed with very irregular distribution in the basal

ganglia, pons, peduncles and medulla. These foci have as a basis, preferably the veins, although in some of the cases an artery would be seen involved. Fatty degeneration of the cells in a focus was frequently seen and in one case severe fatty degeneration of the capillaries. The foci were composed of polyblasts, lymphocytes and plasma cells. No plasma-celled infiltration of the cortical capillaries was observed, but plasma-cell infiltration of the capillaries in the localities near foci, as in the pons, peduncles, etc., was very general and widespread. A very marked feature in all of the cases was the swelling and active proliferation of the endothelial cells of the bloodvessels with its frequent desquamation sometimes to such an extent that it blocked the vessels. Polynuclear leukocytes were frequently present in large numbers in the lumina of the vessels.

Nerve-cell injury was very variable and in general of the character and extent which is caused by severe edema.

Glial reaction was extremely limited except in those cases in which older foci of degeneration were seen.

Case III was extremely interesting from its negative diagnostic value as meningo-encephalitis tuberculosa and meningo-encephalitis lethargica could be absolutely excluded, whereas the picture of severe degeneration of the nerve cells without axonal reactions and the progressive and regressive changes in the glial structure is that seen in tetanus.

Case X offered a very characteristic picture of severe general paralysis of the insane, probably rather acute in character; moderate to severe generalized leptomeningitis with plasma cells in the majority in the infiltrate with a compliment of small lymphocytes, a few polyblasts and many mast-cells, no large phagocytes or giant-cells. There was generalized infiltration by plasma cells of the capillaries in all parts of the brain studied. There was much increase in all glial elements and many rod cells were present.

The fact that the cytological architectonic of the cortex was not altered and that the degeneration of the nerve cells was more moderate in character than usual in general paralysis of the insane was probably due to the acuteness of the attack and its limited duration of time.

Case II stood alone pathologically, the most marked feature being the very severe degenerative and the marked regenerative processes in the bloodvessels, the degeneration leading to hemorrhages and softening of the tissues, and the regeneration to a great excess of connective tissue around the bloodvessels. In addition, a direct invasion of the tissues of the lenticular nuclei by polynuclear leukocytes, the whole giving the picture of encephalitis of the basal ganglia, probably of streptococcic origin. The absence of purulent meningitis, which might have been anticipated in this case, is notable.

Summary. From this brief study can one draw any conclusions as to the variety of encephalitis or meningo-encephalitis from

the localizing symptoms present? That question must be answered in the negative, since localization of the foci in the 3 cases of tubercular meningo-encephalitis, where practically all the nuclear areas in the basal ganglia and the central gray matter about the aqueduct, etc., showed foci in much the same location and extent as those seen in the cases of lethargic encephalitis. The same holds true for the presence of tremors, choreiform movements, etc., as in all the cases of encephalitis studied here included Cases I, II, IV, V, VI, VII, VIII, IX and XI, foci of inflammation or degeneration were seen so widely, diffusely and irregularly scattered that no conclusions as to localization of symptoms could be drawn.

The important question still remains: Are there definite pathological pictures of the various forms of meningo-encephalitis?

Tubercular meningo-encephalitis may be cited affirmatively as even in the absence of tubercle bacilli, which are not always easy to demonstrate, the severe meningitis with plasma cells, small lymphocytes, giant-cells, but more especially the predominence of giant phagocytes renders a diagnosis easy.

General paralysis of the insane with a more or less severe meningitis with plasma cells, mast-cells, lymphocytes, the absence or rare appearance of giant phagocytes, the presence of generalized plasma-cell infiltration of practically all the capillaries in the cortex of a brain area, and the presence of large numbers of rod cells renders a diagnosis easy.

Left for consideration, then, is lethargic meningo-encephalitis. In acute cases certain points stand out: The involvement of the veins in the inflammatory process, to the exclusion of the arteries; the very slight connective-tissue reaction or its complete absence; the presence of fat in the cells of the foci and in the vessel endothelial cells and the minimal amount of reaction in the glia. The cases here reported illustrate these points. But in cases of more chronic character or cases dying months or years after the acute process has ceased, the above diagnostic points are bound to disappear. This is shown by the old foci seen in some of these cases where, with their increase in connective-tissue and glial tissue, they are indistinguishable from encephalitic foci of many other origins. The importance then of most careful *clinical*, *serological*, *bacteriological* and *pathological* study of all avaiable cases cannot be too strongly urged for the purpose of obtaining clearer views of *etiology*, *pathology*, *symptomatology*, *course* and *prognosis*, immediate and remote, of the disease, with the ultimate goal of its *prevention* and *treatment*.

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THE ACCURACY OF THE CAT METHOD FOR THE ASSAY OF DIGITALIS.

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During the winter of 1916 and the early spring of 1917, a number of tinctures, made from digitalis leaf, grown in the vicinity of Richmond by Mr. J. W. Wilber were assayed in our laboratory by the one-hour cat method of Hatcher and Brody. On account of the unusual potency of these samples, they were kept in order to determine the effect of age; and in 1922, they were retested by the cat method. The results which were obtained on this second assay appeared to indicate that certain of the tinctures had deteriorated; while others retained their strength unaltered. This was indeed surprising, in view of the fact that the samples were originally of approximately the same strength; were all made from the same variety of leaf; and had been extracted and preserved in the same manner. Further investigations, carried out not only on these samples but on other tinctures and on solutions of ouabain have convinced us that the apparent deterioration of the original samples may be explained by the recognition of imperfections in the method of assay as applied by us. In order to make this clear, it will be necessary to give the details of our tests.

In carrying out the assays by the cat method, the technic described by Hatcher and Brody has been followed with only slight modifications. Only full grown, apparently healthy cats have been used; and lactating and pregnant females have been eliminated where the amount of digitalis required to cause death has differed from the average for that particular sample. In most cases, ether has been used for anesthesia; occasionally, chloretone has been given orally or intraperitoneally. In a few cases, the combined method, making use of ouabain, was employed; generally, the diluted tincture alone was slowly injected until death occurred. The rate of injection was about 0.5 cc every minute.

From the results of the assays, the tests may be placed in three classes: First, those in which the cats showed no marked individual variations in their resistance; second, where, in spite of decided individual differences, the averages of the different series agreed closely; and, third, where repeated tests gave discordant figures.

As illustrative of the first class, sample No. 36 may be cited. This sample was first tested in February, 1917; only two cats being

used; the lethal doses were 41.5 and 43.0 mg. per kg. respectively. In May, 1922, the sample was again assayed; three cats being used, and the lethal doses were found to be 43.63, 41.2 and 42.07 mg. per kg. respectively. The difference between the smallest and the largest dose is seen to be less than 6 per cent; while the averages of the two series check almost exactly (42.25 and 42.3).

In discussing the technic of the cat method, Eggleston has said: "It is, therefore, obvious that one must not trust the reaction of a single animal. . . . In carrying out the cat method of standardization in actual practice, at least three animals are used, and if all three give closely similar results, the average is taken as being correct. If two of the results are quite close, but the third is considerably at variance, a fourth or even a fifth test is made before an average is struck."

Moreover, before calculating the average for a series, this author states, with justice, that obviously abnormal animals should be eliminated. It has been our experience that, following these directions, it is often possible to secure concordant results in the face of considerable individual variation of the animals used. This is shown in Table I, containing a summary of the different assays of sample No. 39.

TABLE I.—DIFFERENT ASSAYS OF TINCTURE NO. 39 BY CAT METHOD.

Date of assay.	Lethal dose, mg. x kg.	Average
Feb. 3, 1917	68.6	
3, 1917	65.2	
14, 1917	77.8	71.25
14, 1917	73.4	
Jan. 24, 1921	79.2	
24, 1921	67.5	
27, 1921	69.3	72.00
27, 1921	102.0*	

One would infer that the fourth cat used in 1921 was abnormal in reaction; after eliminating this animal, in spite of a not inconsiderable difference among the individuals of the two series, the averages agree within less than 2 per cent.

Unfortunately, with us, it has not always been possible to secure such happy results. Thus, in assaying sample No. 34, two cats were used on March 10, 1917; the doses required being 54 and 40 mg. per kg. respectively. Four days later, two more cats were used; the doses necessary at this second assay were 72 and 70 mg. per kg. On March 16, another pair of cats gave figures of 62.2 and 66.7 mg. per kg. respectively. The second and third pairs gave averages differing by about 9 per cent; while the larger dose of the first pair differs more than 23 per cent from the average of the second pair. But still more disappointing results were secured when

* The averages are calculated after eliminating this experiment.

this sample was tested in 1922 and 1923. These results are given in Table II.

TABLE II.—ASSAYS OF TINCTURE NO. 34 BY CAT METHOD.

Date of assay.	Lethal dose, mg. x kg.	Average.
June 15, 1922	41.1	
15, 1922	62.3	64.23
15, 1922	89.3	
19, 1922	104.7	
19, 1922	99.4	
Feb. 10, 1923	80.0	
10, 1923	87.8	
10, 1923	112.8*	82.36
10, 1923	79.3	
26, 1923	101.0*	
26, 1923	86.0	
26, 1923	96.9*	86.75
26, 1923	87.5	
Mar. 28, 1923	62.2	
28, 1923	74.3	68.25
29, 1923	58.2	
29, 1923	66.4	62.30
29, 1923	105.6*	

The average of the three pairs of cats used in 1917 was 60.8 mg. per 1 kg. The three cats used on June 15, 1922, gave an average not far from that of the initial assays; but three days later a pair of cats gave the fairly closely checking figures of 104.7 and 99.4 mg. per 1 kg. Of the four cats used on February 10, 1923, one would infer that number three was abnormal; after its elimination, an average of 82.36 is obtained. Sixteen days later, serious difficulties are encountered. Of the four cats used on that date, which are "abnormal"? Two check quite closely at 86.0 and 87.5; while two others give values of 101 and 96.9, neither one of which differs more than 2 per cent from their average. However, if we accept the two smaller figures, an average of 86.75 is secured; agreeing fairly well with the assay carried out earlier in this month and indicating a definite loss in the strength of the tincture. On March 28, however, the two cats used appear to show that the tincture is regaining its strength, and this is apparently confirmed by the tests carried out the following day, if we eliminate the supposedly abnormal cat that required 105.6 mg. per 1 kg. to cause its death.

Eggleston[1] has recognized the chance of two cats in the same series being "abnormal" in a similar direction, but he considers this

* The averages are calculated after eliminating these experiments.

[1] Biological Standardization of the Digitalis Bodies by the Cat Method of Hatcher. Am. Jour. Pharm., 1913, **85**, 99.

"an almost impossible accident." As has been pointed out, this actually occurred in the tests of No. 34 on February 10, 1923, and our records show that a similar accident has occurred in the assay of other samples. These instances have been collected and placed in Table III. It is to be understood that, in most cases, a much larger number of cats were used in each assay; we have selected only the ones illustrating our point.

TABLE III.—ASSAYS SHOWING CHECKS AT DIFFERENT FIGURES.

No. of sample.	Lethal dose, mg. x kg.	Total number of cats used.
9	47.8 48.0 82.0 86.0	13
11	62.8 67.0 102.6 127.7	12
33	61.5 61.6 87.1 87.7	6
45	60.5 61.3 81.6 81.7	9
47	28.2 26.8 48.5 49.7 60.3 60.6 60.7 61.0 67.0 67.8 72.0 72.7 81.5 81.6 92.3 92.5	36
60	46.0 47.0 56.6 57.8	6

In justice to the method, attention must be called to the fact that in most cases, these "abnormal" pairs did not come in the order in which they are placed in the table; they were usually separated by results closer to the average. Nevertheless, they did occur; in some instances, in such order as to lead to the most erroneous deductions.

To what are these undesirable results attributable? Hatcher and Brody[2] have called attention to the fact that certain tinctures show considerable precipitation on dilution with saline. This could scarcely explain our results, since the same procedure was followed in each assay, and precipitation, if it exerted any influence, should have led to a constant error. Furthermore, no decided difference could be observed when the "combined method" of assay was resorted to.

Sex, apparently, does not affect the reaction of cats to digitalis. This is illustrated by the figures in Table IV, where the averages for those samples assayed on at least two cats of both sex are given.

TABLE IV.

No. of sample.	Assay on male cats, mg. leaf x kg. cat.	Assay on female cats, mg. leaf x kg. cat.
9	65.68	60.45
11	68.26	65.94
33	64.10	62.32
34	71.76	74.48
36	42.30	43.97
39	70.46	75.40
42	58.70	67.86
43	60.40	68.63
45	73.25	73.00
47	62.44	65.94
52	66.06	62.74
S.-P.	54.30	43.50

Eggleston has shown that season may affect the resistance of cats to digitalis poisoning. According to this author, greatest individual variability is to be encountered in the hot months of July and August, but, while we are able to confirm his observation as to variability of cats at this time of the year, we have not found that such differences occur exclusively in the summer months, as may be seen by reference to the figures for the February and March assays of No. 34 (Table II).

Conclusions. It is not our desire to create the impression that the cat method of assay is valueless; on the contrary, it is our personal opinion that it excels other methods for the physiological standardization of digitalis. The impression that appears to prevail in some quarters is that two or even a single cat suffices to determine with extreme accuracy the strength of a digitalis preparation, and this in spite of the definite statements to the contrary made by Eggleston. Our own observations offer additional evidence that only by the use of large numbers of cats can this accuracy of standardization be attained and, naturally, cast some doubt on the statements that have been made regarding deterioration of tincture of digitalis as judged by the cat method of assay.

[2] Biological Standardization of Drugs, Am. Jour. Pharm., 1910, **82**, 360.

PAROXYSMAL VENTRICULAR TACHYCARDIA: REPORT OF A CASE LASTING ONE HUNDRED AND FIFTY-THREE HOURS WITH RECOVERY.

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The prognostic significance of paroxysmal ventricular tachycardia makes its recognition of definite importance. Judging from the small number of cases reported, seemingly it is one of the rarest disturbances of cardiac mechanism. Its differentiation from paroxysmal auricular tachycardia is important and will become more universal because of the increased use of the electrocardiograph.

The case here presented is of prime interest in that it again emphasizes the association of paroxysmal ventricular tachycardia with grave myocardial disease; in that the patient survived an attack of unusual duration; and in that the electrocardiograms showed independent auricular activity with unusual clearness.

Case Report. W. T. W., a white male, aged forty-six years, was admitted to the medical division of the Lewis-Gale Hospital, December 12, 1922, complaining of shortness of breath, chiefly nocturnal, precordial pain, and swelling of the lower extremities and abdomen. He stated that his illness began on May 5, 1922, when he was awakened by violent pain in his chest which radiated to both arms, especially the left arm. His family physician who was with him stated that no relief being obtained from hypodermics of morphin, chloroform was administered. The attack lasted for eight hours, during which period cyanosis was marked, and the patient presented many aspects of impending death. Since that time the patient has been unable to attend to any of his duties as a minister because even moderate exertion brought on recurring attacks of angina and dyspnea. One month before the onset of his illness his blood-pressure was 160–90.

Previous History. The patient gave a history of having had measles, mumps and pneumonia, and one year previously influenza. With the attack of influenza there was an infection of the left maxillary sinus. This was drained and was cured. He had frequent attacks of migraine prior to the original attack of angina but since then had been free from headache.

Physical Examination. The physical examination showed slight cyanosis with moderate respiratory distress. There was distinct venous distention in the neck. The heart was definitely enlarged, with a transverse diameter of 19 cm. No murmurs were heard. The cardiac rate was 98. Aortic dulness was increased. The systolic blood-pressure was 122, the diastolic blood-pressure was 100.

Moist rales were heard in bases of both lungs. The liver was 6 cm. below the costal margin in mid-clavicular line and there was marked tenderness over it. There was slight ascites with considerable edema over the sacral area and lower extremities.

Laboratory Examination. Examination of blood and urine showed nothing of importance. Wassermann reaction, negative; blood urea, 41 mg. per 100 cc.

Roentgen-ray of chest, 7-foot plate: Transverse diameter of chest, 31½ cm.; heart, 19 cm.; aorta, 9 cm.

Electrocardiograms: Fig. 1 showed ventricular complexes of a distinctly abnormal type. There is a slight widening of the *QRS* complexes, isoelectric *T* wave in Lead II, notching of *P* wave in Leads I and II.

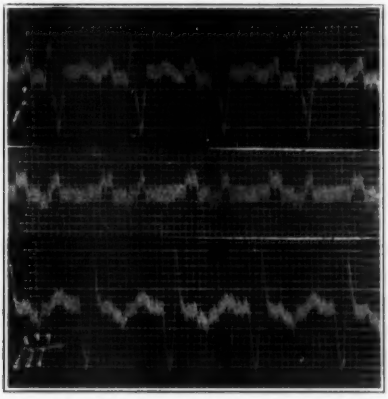

FIG. 1.—Taken December 14. No disturbance in rhythm is noted.

Course in Hospital. The patient remained in the hospital for four weeks during which time his clinical condition improved. The edema lessened and many of the signs of congestive heart failure disappeared. During his stay in the hospital he had several mild attacks of angina, but none severe enough to require morphin for relief. The patient returned home, but on March 1, 1923, was readmitted to the hospital. At this time there was marked ascites and edema of the lower extremities and scrotum. The patient stated that he had been bedridden since leaving the hospital. He also stated that recently his abdomen had become markedly swollen and that paroxysmal palpitation had become very troublesome. On the day of his admission he began with one of his attacks of so-called palpitation.

Physical Findings. There was extensive edema of body, scrotum and extremities and the veins in the neck were full and pulsating.

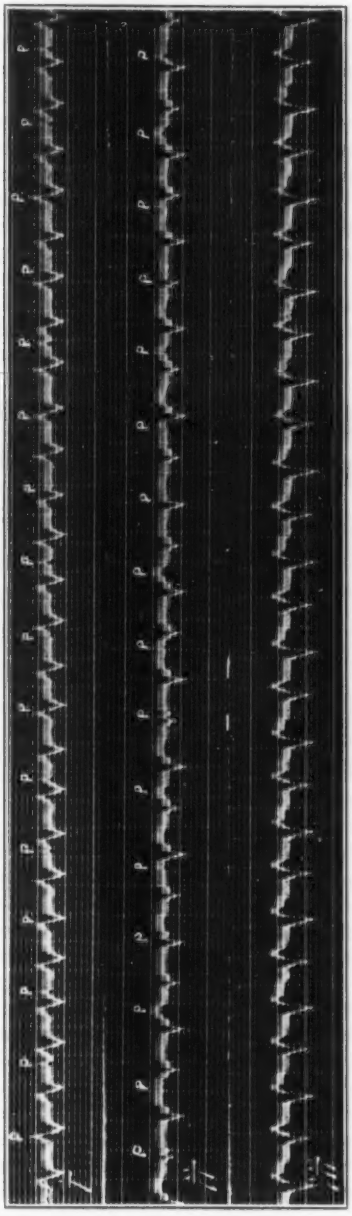

FIG. 2.—Taken March 2, 1923, on second day of the attack. Ventricular paroxysmal tachycardia. Auricular rate, 120; ventricular rate, 204.

The heart was markedly enlarged but because of existing body edema, borders could not be accurately demarcated. The cardiac rate was very rapid, 190 plus, and apparently regular. The pulse was small, compressible and arrhythmic. Blood-pressure was 80. The abdomen was markedly distended with ascitic fluid. The attack of tachycardia lasted until the evening of March 7, a period of six days and nine hours from the onset.

The electrocardiogram (Fig. 2) was taken on March 2. During the attack of tachycardia many tracings were made, but the one selected best illustrates the type of cardiac action observed.

Electrocardiogram: Ventricular paroxysmal tachycardia. An independent auricular activity is easily recognized in Leads I and II, rate 120; ventricular rate 204. There is a peculiar alternation of the ventricular complexes in all leads, especially marked in Leads II and III.

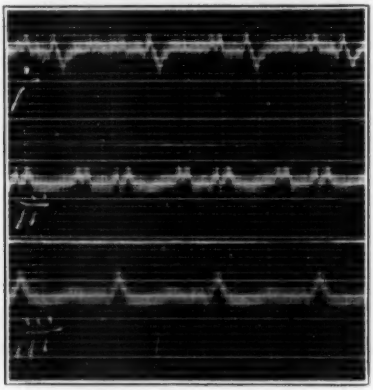

FIG. 3.—Taken March 9, 1923, two days after the cessation of the paroxysm.

On the second day after the cardiac mechanism had returned to normal there was aspirated from the peritoneal cavity 3000 cc of ascitic fluid.

An opportunity to make further electrocardiographical studies since March 9, 1923, (Fig. 3) which was the day after the cessation of the tachycardia, has not been afforded, but the patient has been observed in his home in several attacks of tachycardia, one lasting thirteen hours or more. Frequent extrasystoles, apparently of ventricular type, are noted daily. At this date the patient is in the terminal stages of cardiac failure.

Discussion. Robinson and Herrmann[1] have stressed the association of paroxysmal ventricular tachycardia with coronary occlusion. One of the cases reported by these observers had an attack lasting apparently eleven days, and lived for a few days after the cessation of the paroxysm.

The case here presented undoubtedly had a coronary thrombosis at the onset of the cardiac failure dating from the attack of prolonged and severe angina pectoris. From that date the patient was never able to regain sufficient cardiac reserve to enable him to "carry on" with any degree of efficiency or comfort. The clinical progress of the case was that of a progressive myocardial disease.

One is safe in inferring, from a study of the cases reported and from the evidence presented in the case here studied, that paroxysmal tachycardia of ventricular origin is invariably associated with advanced and grave myocardial disease.

The clinical recognition of any phenomenon either of cardinal diagnostic importance, or of positive prognostic significance is always desirable. Strong and Levine[2] emphasize the importance of ventricular irregularity as an aid in the bedside recognition of this disturbed mechanism. They point out the importance of prolonged auscultation in the recognition of this irregularity. Ventricular irregularity can be detected in most, if not all, of the tracings of the reported cases. It must be admitted, however, that while this irregularity is apparent on the cardiograms its auscultatory detection will be most difficult. With a rate of 190 or more the diastolic period is so markedly abbreviated that an irregularity of a degree capable of clinical recognition is not very probable.

Wolferth and McMillan,[3] in a recent report of 4 cases, have reviewed the literature of the previously reported cases. They outlined the cardinal principles which should guide one in the recognition of paroxysmal ventricular tachycardia. The positive recognition of auricular activity occurring independently of, and at a slower rate than the complexes of ventricular origin; and of the ventricular complexes presenting distinctly abnormal form, is of supreme importance. The occurrence of isolated ectopic ventricular beats before or after the paroxysm is suggested as a guide to recognition. The case here presented possesses these hall-marks. The attacks occurred in paroxysms and were undoubtedly the cause of the paroxysmal palpitation. If this be true this patient had a large number of recurring paroxysms. Independent auricular activity is easily recognized in leads I and II of the electrocardiograms. The tracings show a perfect dissociation of auricular and ventricular activity, the auricles beating at an independent rate of 120, the ventricles beating at a rate of 204. Ectopic beats of ventricular origin were frequently observed though not recorded graphically.

The effect of prolonged ventricular activity on a heart already severely damaged by degenerative processes is of particular clinical interest. Barcroft, Boch and Roughton[4] have studied the circulatory condition existing in a state of paroxysmal tachycardia. Their conclusions were:

"1. In two attacks of paroxysmal tachycardia in which the pulse was upward of 200, the minute-volume sank from 5 to 6.1 liters to

2.8 to 2.1 liters per minute, or roughly, to half to a third of the normal volume.

"2. The degree of ischemia was particularly marked in the skin, as shown by analysis of the blood from the basilar vein.

"3. There was no reduction in the saturation of the arterial blood, but if anything a rise.

"4. The depth of the respiration was reduced to nearly half the normal while the rate was about doubled.

"5. The systolic output 77.5 to 12.9 cc.

"6. The total oxygen consumption of the body was also considerably lowered during two of the attacks."

Carter and Stewart,[5] in their study of a case of paroxysmal tachycardia, are somewhat at variance with these conclusions. They found a marked decrease of oxygen saturation of the arterial blood. A stagnant anoxemia due to slowing of the circulation brought about by the tachycardia through a greatly decreased output per beat was noted by both groups of observers.

The most noticeable change in the patient here studied, clinically, was a rapid increase in the anasarca with a reduction in urinary output. There did not appear to be any appreciable increase in the degree of respiratory distress. The respiratory rate remained between 20 and 28 per minute.

Cardiac pain was entirely absent during the period of the paroxysm. This is of interest in connection with the consequent lowering of aortic pressure due to the diminution of ventricular output. The highest systolic reading during the attack was 80. The lowest was 65. The systolic and diastolic pressures were incapable of differentiation. Only one single beat marked the auscultatory sounds over the brachial artery. On the second day after the cessation of tachycardia the systolic blood-pressure was 110 and the diastolic was 100.

The prolonged period of the paroxysm offered an excellent opportunity for trying the effect of various remedies and procedures. Vagus pressure did not appear to influence the rate. The only suggestive positive effect was obtained with quinidin sulphate. Quinidin sulphate 0.4 gm. was administered by mouth at 9 P.M., 11 P.M., and 2 A.M. on the night preceding the cessation of the paroxysm. Its influence can be only speculative. Singer and Winterberg[6] report its successful use in paroxysmal ventricular tachycardia. Owing to the apparent influence on the paroxysm the patient continued the use of 0.4 gm. twice daily. The patient himself felt that his palpitation was greatly decreased by the remedy. It is of interest to note that the only other prolonged attack, which lasted apparenly thirteen hours, occurred after the abolition of quinidin for one week.

Conclusions. 1. A case of paroxysmal ventricular tachycardia of unusual duration is presented. Again emphasized is the association

of this disturbance of cardiac mechanism with grave myocardial disease, especially coronary thrombosis.

2. The electrocardiogram shows the dissociated auricular activity with unusual clearness. The tracing also presents an unusual alternation of the ventricular complexes.

3. The therapeutic value of quinidin sulphate in paroxysmal ventricular tachycardia is debatable. It is tenable that good may come of its further study and usage.

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A CASE OF TRYPANOSOMIASIS TREATED WITH TRYPARSAMIDE.

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Introduction. Cases of African sleeping sickness, or trypanosomiasis, are rarely seen in temperate climates and an opportunity for making a careful study of either the manifestations of the disease or its treatment is seldom afforded. Moreover, the present case is of interest because of the fact that the patient was treated with "Bayer 205" and with tryparsamide. Both of these drugs have aroused a great deal of interest on account of the favorable results which have been reported from their use in trypanosomiasis. Exceptionally good results have also been reported from the use of tryparsamide in neurosyphilis. It is for these reasons that the following case report is published.

History Report.—Case (History No. 4707), female, aged forty-one years, white, missionary. Admitted February 26, 1923; discharged May 24, 1923.

Summary. Onset in the Belgian Congo, October, 1919, with attacks of fever associated with lassitude and asthenia. Crescentic and annular erythematous rash and general glandular enlargement noted in December, 1919, while en route to the United States. The

rash disappeared after eight months, but the glandular enlargement persisted, together with undernutrition and asthenia. Generally "weak and run down" during 1920 and 1921. Bilateral otitis media and antrum infections. In February, 1922, her weight was only 42.2 kg., and there developed increasing asthenia, diplopia, ataxia, general tremulousness, drowsiness and amenorrhea. Disturbance of the senses of taste and smell. Steady failure until July, 1922, when, after the demonstration of Trypanosoma gambiense in blood, lymph gland and cerebrospinal fluid, she received 3 doses of atoxyl. Progress of disease apparently arrested. Ten doses of "Bayer 205" with steady improvement, so that in December, 1922, she was symptomless except for slight asthenia and anorexia. Weight 50 kg. In January, 1923, a relapse occurred, with return of former symptoms, together with "lightning" pains in shoulders and symptoms suggestive of mental deterioration. Her weight on admission was 43 kg. Physical examination revealed moderate secondary anemia, extremely dry skin, general glandular enlargement, pyorrhea alveolaris, blood-pressure 80/60, splenomegaly, tremor of tongue, facial muscles and extremities, general muscular weakness, positive Romberg's sign and unsteady gait, poor coördination of movements of extremities, hyperactive deep reflexes, slight muscular rigidity, poorly sustained left ankle and patellar clonus, positive Babinski's sign on the left side, and somnolence. Temperature 99.5° to 102° F. Blood, cerebrospinal fluid and extirpated lymph node negative for trypanosomes. Cerebrospinal fluid contained 30 cells per c.mm. and globulin. Wassermann tests on blood and cerebrospinal fluid negative. Symptoms unabated for a period of three weeks, at end of which time a course of 10 doses of tryparsamide was given, with prompt subjective and objective improvement. Spinal fluid changes slight. Has remained symptomless to date.

Complaint. The patient complained of weakness, unsteadiness and drowsiness.

Family History. Her family history was unimportant.

Past History. Her general health has been good. She had measles, mumps, chicken-pox, and pertussis during childhood. At the age of ten she had typhoid fever from which she recovered without complications. There have been no other diseases and, until onset of the present illness, she has enjoyed unusually good health. Her menstrual periods began at the age of thirteen years; they were at first accompanied by pain but soon became normal.

She married a missionary in 1910 and went with him to the Belgian Congo in 1911. After about six months she returned to the United States where a baby was born in 1912. This child died at the age of seven months from an undetermined cause. In 1912 the patient was rejoined by her husband and they lived in New York until 1914, when a second child was born. The latter is living and well. In 1916 the couple returned to the Belgian Congo.

Present Illness. The first symptom referable to the present illness was noted in 1919. Prior to this time her health had remained good in spite of the conditions under which she lived. Her usual weight was 120 pounds. However, in October, 1919, a very definite change in her health occurred. Within a period of two weeks she experienced three febrile periods, each lasting from three to four days. During these attacks her temperature reached 103° to 104° F. The attacks were separated by afebrile intervals of from one to two days. Because of the fever, she left her station, Tshumbiri, on the Congo River, and returned to Kimpese, from which point, after about two weeks of weakness and lassitude, she went to a port and boarded a steamer for the United States, *via* Plymouth. In December, during her voyage home, the patient thinks that she had no fever. She felt weak, however, and noted that lymph nodes in the neck, axillæ, and groins were enlarged. At this time a curious skin eruption appeared over the back and abdomen; the lesions were erythematous, and were annular or crescentic in shape. The usual lesion was a partial or complete circle of red, mottled skin surrounding a perfectly normal central area. These circles, or crescents, varied from 5 to 8 cm. in diameter, were not elevated, and caused the patient no discomfort.

On her arrival in the United States in January, 1920, the patient did not consider that she was sick, although the skin eruption and glandular enlargement persisted. She was sent to a hospital for the routine examination required by her Missionary Board and was told that, except for slight anemia, she was in good condition. No explanation was offered as to the cause of the skin rash and adenopathy. During the remainder of 1920 the patient lived in Chili, N. Y., and was occupied with the usual duties of a housewife. The rash disappeared after about eight months. She had, during this period, bilateral otitis media and antrum infections which cleared up slowly. She "was not strong" and attributed the feeling of weakness and of lassitude to her previous stay in Africa. The menstrual periods were regular. In February of 1922 there was a change for the worse. Asthenia and anorexia became more marked, and her weight was reduced to 42.2 kg. Amenorrhea developed. She first noted drowsiness and diplopia at this time. Unsteadiness of station and gait developed, together with a coarse tremor of the extremities. The sense of taste and of smell became impaired. Because these symptoms continued to get worse, in July she visited a western clinic where Trypanosoma gambiense were found in the blood, in a lymph node, and in the cerebrospinal fluid. She was given 3 doses of atoxyl and advised to go to a London hospital for further treatment. She arrived there in August, 1922, and received 10 intravenous treatments of "Bayer 205."[1] There was marked improvement in all symptoms and she returned to the United States in November, 1922, feeling well. She had gained 3.5 kg. in weight,

the tremor and drowsiness had disappeared and her gait was quite normal. The sense of taste and of smell had returned, and the menstrual periods were reëstablished. Her appetite was rather poor. She again took up her household duties.

In January, 1923, she experienced a return of most of her former symptoms, including weakness, unsteadiness, drowsiness, impaired sense of taste and smell, amenorrhea, anorexia and loss in weight. A new symptom developed in the form of severe "lightning" pains in both shoulders and arms. On admission to this hospital on February 26, 1923, she complained of the symptoms enumerated above and also that her memory was poor. She felt that her whole personality had changed. She was depressed and, though her insight was good, she was indifferent as to the outcome of her illness.

Physical Examination. Temperature 99.2° F., pulse 80, respiration 20. Height 156.5 cm. Weight 43.6 kg.

She was a well-developed, poorly-nourished, pale, white woman, who appeared to be about forty-eight or fifty years of age. She was indifferent and apathetic. Insight as to her condition was good and she coöperated fairly well throughout the examination, though it was with difficulty that she remained awake. The skin over the entire body was dry and atrophic. Over the hands and feet the skin was also thick, shiny, darkly pigmented, and somewhat scaly. No gauntlet effect was present. There was no rash. The mucous membranes were pale but otherwise normal.

The cervical, axillary and inguinal lymph nodes were easily palpable, averaging 1.0 to 1.5 cm. in diameter, and were firm and somewhat fixed; they were not tender. Small, firm epitrochlear lymph nodes were palpable.

All the upper teeth and the lower right molar teeth had been extracted. The remaining teeth showed marked pyorrhea.

An examination of the lungs was negative. A soft systolic murmur was heard at the apex of the heart. The peripheral bloodvessels were soft, the pulse small, and the blood-pressure 80/60.

The spleen descended to the costal margin on deep inspiration and was rather soft. The lower poles of both kidneys were palpable.

Neurological Examination. An ophthalmoscopical examination revealed no abnormalities. A marked tremor of the muscles of the face, particularly of those about the eyes, was present. The tongue showed a rather coarse tremor. Otherwise the examination of the cranial nerves was negative.

A marked general weakness was present. No weakness or paralysis was noted in special muscle groups. The patient stood with feet well apart and took short, uncertain, hurried steps. Romberg's sign was slightly positive. Coördinated movements were poorly performed. No disturbances were demonstrated in the sense of touch, pain, or temperature. Deep hyperesthesia was present over the long bones. The deep reflexes were moderately

hyperactive. There was slight muscular rigidity. Babinski's sign was positive on the left side and negative on the right. A poorly sustained clonus of the left ankle and patella was obtained. The abdominal reflexes were present.

Laboratory Examinations. Urine: Specific gravity: 1010-1018. Reaction: acid. Albumin: negative, or only trace. Sugar: negative. Microscopical examination: negative.

Phthalein excretion: first hour 40 per cent; second hour 12 per cent; total 52 per cent.

Blood: Red blood cells, 4,672,000; hemoglobin, 82 per cent (Sahli); white blood cells, 9800.

Differential count (in percentages): Polymorphonuclears, 67.0; basophiles, 0.5; eosinophiles, 6.0; large lymphocytes, 7.0; small lymphocytes, 16.5; large mononuclears and transitionals, 3.0.

Stained film: Erythrocytes showed slight central pallor. The platelets were unusually large. Several examinations of "thick" preparations revealed no parasites.

Wassermann reaction (blood): negative.

Cerebrospinal fluid: Pressure not increased. Cells, 20; globulin, + +. Wassermann reaction (2 cc), negative. Colloidal gold curve, 2224331000. Parasites in centrifugalized sediment, none.

Roentgen-ray of skull, chest and tibiæ, negative; basal metabolic rate, normal; stool examination, negative.

One specimen of blood, 2 of cerebrospinal fluid, and an emulsion of an extirpated axillary lymph node were injected into guinea-pigs, rats and mice; these animals remained normal and, while under observation, showed no evidence of trypanosome infection.

Course in Hospital. For a period of twenty-three days the patient was kept in bed on a full diet with extra nourishment. No drugs were administered during this time. On this regime she gained 2 kg. in weight. However, her mental condition showed but little improvement. She remained indifferent and apathetic and had intermittent mild headaches. At times during this period she became a little brighter, but in the main she was dull and drowsy. Her appetite was poor; she had to be fed by a nurse because of weakness. She was careless of her personal appearance. She rarely talked to the nurses or attendants. The pains in her shoulders persisted, but were not so severe. Curious jerking movements of the left thigh were noticed. The tremor and poor coördination persisted, and fever was present. A second lumbar puncture, performed on March 15, showed: 30 cells, globulin + + +, and no parasites.

On March 20, 2 gm. of tryparsamide were given intravenously. As will be seen from Chart I, the temperature immediately fell to normal. A remarkable change in the mental condition was noted during the following week. She became much brighter, more interested in her surroundings and in her personal appearance. She spontaneously engaged in conversation, was less drowsy, and her

appetite improved so that she began to look forward to her meals and to feed herself.

During the period between March 20 and May 21 the patient received 10 doses of tryparsamide intravenously, a total of 23.0 gm. of the drug being given. Improvement was continuous. Her personality changed from that of a depressed, indifferent, careless, lethargic individual, to one of a bright, interested, talkative, optimistic woman. The tremor of the face and extremities slowly disappeared. The headaches and pains in the shoulders and jerky movements of the left thigh were no longer troublesome. The reflexes became normal and Babinski's sign negative. Her station and gait were now normal. She gained, during this period, 10 kg. in weight, and the menstrual periods returned. The blood-pressure rose to 110/75. The spleen remained just palpable. Cerebrospinal

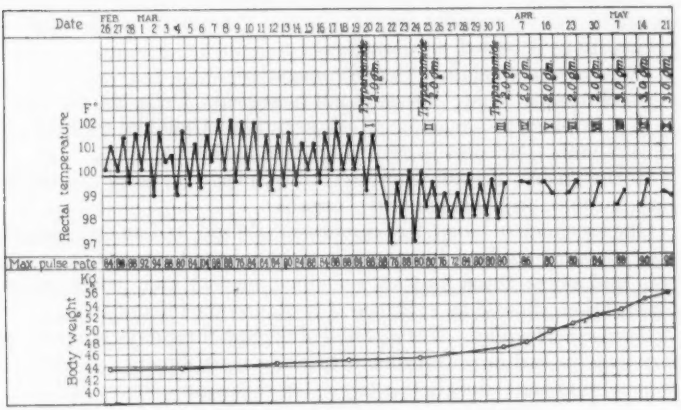

CHART I.

fluid obtained May 3 showed 20 cells and globulin + +. The colloidal gold curve was 2222331000, and the Wassermann reaction negative.

She was discharged, symptomless, May 24, 1923. On July 5, 1923, the patient returned for examination. She had remained entirely symptomless since May except that the last two menstrual periods have been missed. The spleen could still be felt and the deep reflexes were possibly slightly exaggerated. The maximum rectal temperature during the thirty-six hour period of observation was 100.1° F. Except for increase in the hemoglobin (95 per cent) the blood was essentially unchanged. Examination of the cerebrospinal fluid: 12 cells; globulin +; Wassermann reaction negative, colloidal gold curve 2233321000. The urine examination was negative except for a trace of albumin.

Discussion. DIAGNOSIS. On admission to this hospital the case was clinically one of recurrent encephalitis. Since trypanosomes had been demonstrated seven months prior to our period of observation, and at a time when the patient was suffering from symptoms almost identical with those which caused her to come to us, it seemed almost certain that the encephalitis was associated with the trypanosome infection.

In the absence of demonstrable trypanosomes, one is forced to assume either (1) that the organisms were present but in localities not accessible when approached by the ordinary routes, or (2) that the patient no longer harbored them. If the latter possibility held, we must assume that the clinical picture was produced by a degenerative process in the central nervous system, the result of a previously active infection. It would seem from the history that this is unlikely. The rather abrupt recurrence of symptoms in February, 1923, with fever and a marked constitutional reaction, is significant. Moreover, these symptoms were identical with those marking a stage in the disease when infection was known to be active in the sense that trypanosomes were demonstrated. That trypanosomes were not demonstrated in the 1923 relapse, either in an excised lymph gland, the blood, or the cerebrospinal fluid, is not remarkable, when one recalls that during the preceding seven months the patient had received 3 doses of atoxyl and 10 doses of "Bayer 205."

TREATMENT. But slight improvement followed the general therapeutic measure employed during the first three weeks the patient was in the hospital. Treatment with tryparsamide was then started.

Tryparsamide is the sodium salt of n-phenylglycineamide-p-arsonic acid. It was first made in 1919 by Jacobs and Heidelberger.[2,5] It was shown, by Pearce and Brown,[4,5] to possess marked therapeutic activity in experimental trypanosome infections and to be relatively speaking, non-toxic.[6] They concluded that, in the experimental disease, it was superior to many of the drugs commonly employed in the treatment of human trypanosomiasis (atoxyl, arsenophenylglycin, salvarsan, neosalvarsan, etc.) In 1921, Pearce[7] reported favorably upon the action of the drug in 77 cases of human trypanosomiasis caused by Trypanosoma gambiense, and Chesterman[8] has recently reported favorably upon its effect in 40 cases of the disease.

Doses of 2 and 3 gm. of the drug were employed. They were, in each instance, dissolved in sterile distilled water and given intravenously at approximately weekly intervals. No untoward drug reactions occurred and clinical improvement was immediate. The temperature fell to normal, the headache and somnolence disappeared, and the patient became bright and active mentally. The appetite improved and there was a rapid gain in weight and strength. The tremor became much less marked and Babinski's sign dis-

appeared. When she was finally allowed to walk, her station and gait had become normal, her coördinated movements were well performed, and Romberg's sign was negative. The pains in the shoulders gradually lessened in frequency and intensity, and the deep hyperesthesia disappeared. Her color improved and the menstrual periods were reëstablished. When discharged, May 24, and when seen again July 5, the patient seemed practically normal except for some emotional instability. The spinal fluid at the latter date still showed globulin, a slightly increased cell count, and an abnormal colloidal gold curve. She is to write at monthly intervals, and to report in person for physical examination and lumbar puncture every two months.*

The discussion of the mode of action of the drug used in the present case is necessarily purely theoretical. The absence of demonstrable trypanosomes prior to treatment makes it uncertain that the beneficial action of the drug was due solely to its trypanocidal effect. That organisms may have been present in inaccessible regions of the cerebrum or spinal cord seems likely. The feature of foremost importance in the case is the marked improvement obtained with tryparsamide in a patient showing a clinical relapse after treatment with a trypanocidal agent as powerful as "Bayer 205." If it is assumed that the action of the drug was purely trypanocidal in character, its ability to arrest the course of the disease might be accounted for either by the fact that its chemical nature is entirely different from that of the drug previously used, or by the assumption that tryparsamide was capable of developing a high degree of therapeutic activity in the central nervous system. This assumption is supported by both experimental and clinical evidence. However, the possibility that a general, non-specific action of the drug played a role in the results obtained in this case should be borne in mind. It is interesting to note, in connection with this possibility, that Pearce and Brown[4] observed such an effect in experimental animals treated with tryparsamide. These workers noted, moreover, that in experimental spirochetal infections,[9] tryparsamide, while not in itself a powerful spirocheticide, did modify or control the course of the infection. It is possible that this non-specific effect may have been, in part, responsible for the results recently obtained with tryparsamide in the treatment of paresis[10] and one naturally conjectures as to the possible usefulness of the drug in chronic diseases other than those caused by protozoa.

* The patient was readmitted to the hospital October 2, 1923, for a second course of treatment with tryparsamide. At this time she was symptomless and the physical examination was entirely negative. A trace of globulin persisted in the spinal fluid. The cell count was 3 per c.mm. and the colloidal gold curve was negative. She was again admitted to the hospital in March, 1924, and found to be in excellent physical condition.

Prognosis. In the light of the history one is inclined to give a guarded prognosis as to the ultimate outcome of the case. As long as the spinal fluid shows pathological changes, the case cannot be pronounced cured, in spite of the excellent general condition of the patient, and the absence of definite symptoms of neurological disease.

Summary. A report is made of a case of African trypanosomiasis in which a relapse occurred after treatment with atoxyl and "Bayer 205." The results of treatment with tryparsamide are given, together with a brief theoretical discussion of the mode of action of the drug.

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SYPHILIS AS THE CAUSE OF MUSCULAR ATROPHY OF SPINAL ORIGIN.*

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In his lecture on The Syphilitic Muscular Atrophies (which is one of twenty (20) given during 1921 by noted neurologists of the Paris Faculty of Medicine) André Léri[1] makes the statement that progressive amyotrophies are most commonly, if not always, syphilitic in origin. In 1897 Pierre Marie[2] questioned whether there

* Publication authorized by the Medical Adviser, U. S. Veterans' Bureau. The cases on which this paper is based were studied at the U. S. Veterans' Bureau, District No. 3, Philadelphia, Pa., the Episcopal Hospital, Philadelphia, Pa., the Philadelphia General Hospial and the University Hospital of Philadelphia.

[1] Questions neurologiques d'actualité, Paris, p. 259.

[2] Revue neurologique, 1897. Quoted by Léri.

was such an entity as a primary chronic anterior poliomyelitis. In 1903 Léri[3] reported 6 cases of spinal progressive muscular atrophy, all of them syphilitic in origin. Two autopsies showed the diffuse vascular lesions of meningomyelitis similar to those observed and described by Raymond in 1893.

In his remarkable paper entitled Progressive Muscular Atrophy, a Study of the Causes and Classification, with the Report of an Autopsy, read at the meeting of the American Neurological Association in June, 1905, Dana[4] went so far as to say, "I have seen so many cases of progressive muscular atrophy that were so distinctly parasyphilitic, that it seems to me that we might infer that nearly all the atrophies were due to this process." And further on he says, "It will be remembered that the investigation into the syphilitic origin of tabes began with rather modest statistics in its support." We were so much impressed with the following portion of Léri's lecture, that we wondered whether the teaching and the general knowledge of this subject were so much more advanced in France than in this country as to warrant the following statement: "This idea (meaning the idea that spinal progressive atrophy is practically always due to syphilis) is now so banal that cases of syphilitic amyotrophy are no longer reported; it can today be stated with assurance that progressive spinal amyotrophy is as much a syphilitic disease as is tabes. There are many cases of actual tabes in which efforts to prove them of luetic origin have failed, both from the standpoint of inheritance and from that of objective examination of the patient, as well as from that of laboratory studies; this is, however, no reason to deny that tabes is syphilitic in origin. Just about as much is true of progressive spinal amyotrophy."

The writers of this paper can hardly believe that in this country the above idea is so "banal" and generally accepted, that these cases are no longer reported, or that the general practitioners and perhaps even the neurologists, have been so impressed with this fact that in the presence of any amyotrophy of unknown cause antisyphilitic treatment is immediately instituted in every instance. It is of interest at this point briefly to record the opinion of different neurologists as expressed in the American standard text books on neurology.

Spiller[5] in his article on progressive spinal muscular atrophy in Modern Medicine says "Some of the cases supposed to represent progressive spinal muscular atrophy are caused by myelitis, especially the syphilitic form. The inflammation may be almost confined to the gray matter and such being the case, sensory disturbance may be absent. The symptoms then would be those of

[3] Report of the 1903 Congress of Neurologists and Alienists, published in Brussels.
[4] Jour. Nerv. and Ment. Dis., 1906, **33**, 81.
[5] Osler and McCrae, Philadelphia, Lea & Febiger, 1913–15, p. 82.

progressive spinal muscular atrophy, although the lesion would be a diffuse process of inflammatory character."

This same writer,[6] in 1912, wrote a paper on syphilis as a possible cause of systemic degeneration of the motor tract. In this article he reported several cases of muscular atrophy occurring in spinal syphilis. Spiller there said: "There is no objection on *a priori* grounds in accepting syphilis as a possible cause of various diseases of the motor system, as primary lateral sclerosis, amyotrophic lateral sclerosis, and progressive spinal muscular atrophy."

In Church and Peterson's[7] text-book, much used by medical students and practitioners, under the heading Etiology in the article on progressive muscular atrophies, presenting lesions of the spinal gray matter, occurs this sentence, "Since the Wassermann and spinal fluid tests have been available, positive findings in these cases indicate that syphilis is a more common feature, if not an actual cause, than was formerly supposed."

Dana, under the heading of Progressive Muscular Atrophy in the ninth edition of his text-book says "All three types of atrophy may be caused by syphilis, and hence the disease may occur in locomotor ataxia. Usually, however, syphilis causes an atrophy running a rather special course." In a footnote he states: "Among 72 cases, four-fifths were in males, syphilis was present in about one-fifth of the cases," and "on the whole the dominant causes are an occupation strain, syphilis, and some inherited weakness of the affected neurones."

White and Jelliffe[8] under the heading Progressive Muscular Atrophy, says "Here heredity may play a part in the development of a familial form, seen in infancy and also in adults (Bernhardt). It may follow acute poliomyelitis. Other factors, as toxemias, trauma, cold, wet, overexertion, are not definitely established. Occupation atrophies are at times incorrectly included here."

Case Reports. The subject is one of great practical importance and we desire to report the following cases as instances of spinal muscular atrophy due to syphilis:

CASE I.—A white male, aged thirty-three years, a motorman, was examined at the U. S. Veterans' Bureau, District No. 3, on December 20, 1922. He does not use alcohol; he has been married four years and has three children, all of whom are living and well. He had a chancre fourteen years ago. His military history is of no importance except that he suffered from so-called "rheumatism" while in the army.

[6] Syphilis a Possible Cause of Systemic Degeneration of the Motor Tract., Jour. Nerv. and Mental Dis., 1912, **39**.

[7] Nervous and Mental Diseases, Philadelphia, W. B. Saunders Company, 1921, p. 408.

[8] Diseases of the Nervous System, Philadelphia, Lea & Febiger, 1917, p. 413.

Present Illness. This man has complained of pain ever since he has been in the service. The pain he describes as dull, stiff and achy, and at times has been sharp and stabbing, especially in the lower extremities. He also has had relaxation of the urinary sphincter. His libido has been much decreased. He has continued his work as a motorman up to the present time.

FIG. 1.—Showing atrophy of hands, especially the right.

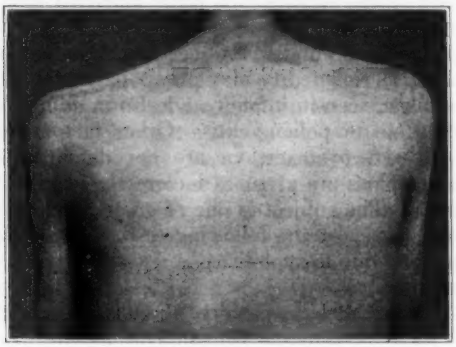

FIG. 2.—Showing atrophy of shoulder muscles.

Physical Examination. The station shows a slight sway but not a true Romberg. The gait is spastic, especially on the right. The deep reflexes in the lower extremities are greatly increased with an abortive ankle clonus on both sides and a typical bilateral Babinski. The deep reflexes of the upper extremities are present, but are greatly diminished. The man's muscular development is very poor, there being a generalized wasting; the small muscles of the hand and the muscles of the shoulder girdle (Figs. 1 and 2)

show real atrophy especially on the right, and marked weakness is present in all four extremities.

Electrical reactions show a marked diminution in the contractibility in response to the faradic current in the atrophied muscles. Fibrillary contractions are present in the muscles of the arms and shoulder girdles. The tongue and lips are not involved. The pupils are equal, slightly irregular and react well to light and in accommodation. All forms of sensation are normal throughout the body. The patient is bright mentally and shows no evidence of cerebral involvement.

On January 5, 1923, the blood Wassermann was strongly positive and the spinal fluid Wassermann was negative. The albumin and globulin were increased in the spinal fluid which showed three cells per c.mm. The colloidal-gold test showed no curve. The roentgenogram of the cervical and upper dorsal spine was negative.

This case, with the exception of the pain and sphincter disturbance, would have passed for a case of amyotrophic lateral sclerosis, the picture of which the man presented. The symptoms came on nine years after the initial lesion, that is, five years ago. From certain facts in the history it is clear that the whole condition is one of syphilis of the spinal cord. Since antisyphilitic treatment has been instituted the patient has greatly improved.

Case II.—A white male, at present aged thirty-nine years, a machinist, was admitted to the Episcopal Hospital on August 14, 1916. His family history was negative. Before his admission to the hospital he used alcohol and tobacco moderately. He had a chancre at the age of eighteen years, in 1902. He was married in 1904 and his wife, who died in 1907, had two miscarriages. This man's trouble began in 1906, the first thing he noticed being weakness of the right hand followed in a short time by wasting of this part and by a wrist drop. The condition then spread to the left hand and wrist, then to the remaining portions of both upper extremities and shoulders, then to the lower extremities and trunk. From the onset until the whole body was involved was eight years. His weight dropped from 172 pounds to 90 pounds.

Physical Examination (February 24, 1923). The pupils are irregular and react poorly to light, but well in accommodations. No cranial nerve palsies are present. The tongue is larger than normal, presenting many deep fissures and resembling the so-called scrotal tongue. The man presents intense atrophy of all muscles from the neck down (Figs. 3 and 4); some of the muscles, especially those of the buttocks are the seat of fibrillary tremors. All of the deep reflexes are lost. Plantar stimulation produces flexion on both sides. No voluntary movements are present in the left upper extremity; in the right upper extremity a little flexion is possible at the elbow with a fair amount of pronation and supination.

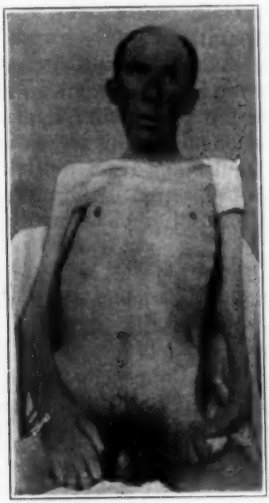

FIG. 3.—Generalized atrophy with deformity.

FIG. 4.—Generalized atrophy with deformity.

The man can turn over in bed, but in so doing he goes through a number of contortions. More power is preserved in the lower extremities than in the upper, movements at the ankles, knees and hips being possible but very weak. The man has a wasp waist. Sensation is normal.

The result of the examination of the eyes by Dr. Fewell on February 28, 1923 is as follows: The discs are dusky and the margins well developed. The smaller vessels are quite tortuous and the veins pressed upon. No lesions of the choroid or retina were seen. The diagnosis is angiosclerosis.

The Wassermann examination of the blood made at the Philadelphia General Hospital, June 12, 1913 was three plus. The blood Wassermann examination at the Episcopal Hospital on March 1, 1923 was negative. The patient has never submitted to a lumbar puncture.

The atrophy in this case began four years after the patient contracted a chancre. His age at the onset was twenty-two, a late age for dystrophy and an early one for progressive spinal muscular atrophy. The condition of his pupils and of his tongue are strongly indicative of syphilis. At one time he had a strongly positive Wassermann although the reaction at present is negative.

Case III.—A Chinaman, aged forty-eight years, was admitted to the Philadelphia General Hospital on December 11, 1920. He was assigned to the service of Dr. Charles S. Potts, through whose courtesy we are reporting this case. The man had a chancre in 1904.

Present Illness. In March, 1920, the patient noticed that he had difficulty in swallowing. Dysphagia progressed so that by the time he was admitted to the hospital he could swallow nothing but liquids. He has lost a great deal of weight.

Physical Examination. Atrophy of the muscles of the upper extremities was present and marked with a great diminution of power in these parts. The lower extremities showed slight atrophy and weakness, but all movements were possible. The biceps, triceps and patellar reflexes were present and increased and a bilateral Babinski was present. Ankle clonus was not obtained. His station and gait, and the finger-to-nose test could not be determined because of weakness. Sensation was normal throughout. The pupils were unequal and irregular and reacted sluggishly to light; weakness of both sides of the face was present. The tongue presented a tremor, was atrophic and could not be protruded. The lips were widely separated; the man could not whistle, and could not blow out a lighted match, and could not talk. He could not swallow solids, and weakness of the soft palate was present. An examination of the spinal fluid was never made, but the blood Wassermann was positive. This patient died on March 19, 1921, and no autopsy was obtained.

This case is one which clinically resembles amyotrophic lateral sclerosis beginning as a bulbar palsy. A clear history of syphilis sixteen years before the onset of the amyotrophia was obtained, and the blood Wassermann was positive. The state of his pupils also pointed to syphilis as the etiological factor in the disease of the nervous system.

CASE IV.—A white male, unmarried, aged fifty-two years, a brass worker for thirty-five years, was admitted to the Philadelphia General Hospital and was assigned to Dr. Charles W. Burr's service October 9, 1921. He died about five months later, on March 19, 1922, while under the care of Dr. D. J. McCarthy, through whose courtesy the report of this case is made possible.

History. The family history was negative; the patient had malaria at thirteen years of age and has had chills and fever at irregular intervals ever since. On admission he complained of loss of power in both arms, pains throughout the arms and legs; headache, loss of power of the lower extremities and loss of bladder and bowel control. A regular rise of temperature in the afternoon was noted. The onset of the condition was in 1913, marked by numbness and tingling in the left hand and with loss of power in the fingers, which gradually involved the muscle groups of the elbow and shoulder. In 1915 the right upper extremity became involved and the atrophy on this side developed rather rapidly. A fracture of the left hip, due to a fall, occurred in 1918 and as a result the left leg has been about four inches shorter than the right. Just before admission, weakness in the legs developed with sharp, shooting pains on both sides. There has been a loss of 20 pounds within twelve months prior to admission.

Physical Examination. The man was found to be much emaciated and had the general appearance of one of seventy rather than of fifty-two. Diplopia was present; the left pupil was slightly larger than the right, and both reacted sluggishly to light but well in accommodation. The left biceps and triceps reflexes were present on the left but on the right side were absent. Both patellar reflexes were absent and there was no clonus. Plantar stimulation resulted in flexion. All the muscles of both arms were markedly atrophied, including the muscles of the shoulder girdle. There was marked diminution in the power of the left upper extremity and the left hand was a typical "main en griffe." There was no motion possible in the right arm except at the wrist and slight flexion of the elbow. Fibrillary tremors were present throughout the muscles of the arm. While there was some atrophy in both legs, it was only slight. Sensation was normal and loss of sphincter control of bladder and rectum was evident. Marked arteriosclerosis with blood-pressure of 180/90 was noted. Kyphosis and scoliosis were present. The cranial nerves were normal. The Wassermann test

of the spinal fluid was four plus. The urine showed some albumin and casts.

Pathology. Microscopically the cord is so small and distorted that it is difficult to distinguish the various levels. The anterior horns are smaller than usual and contain fewer nerve cells throughout (Fig. 5). The least involvement is in the lower lumbar and sacral regions but even here the cells show degeneration. The type of cell change varies—simple atrophy predominates, although lipoid degeneration is present. The glia elements are increased. The anterior roots are degenerated to a large extent (Fig. 6).

FIG. 5.—Anterior horn cells, lower cervica region showing marked decrease in number and many small atrophic cells present with increase in glia nuclei. Kresyl violet, × 80.5.

Clarke's columns are well preserved and stand out in marked contrast to the few and atrophic anterior horn cells. The posterior columns show sclerosis more marked in the upper cord (Figs. 6 and 7). Lissauer's tract is likwise degenerated as are also the posterior root fibers. The lateral columns are uninvolved. The meninges are thickened and contain a few small round cells mainly of the lymphocytic type (Fig. 8) especially noticed around the vessels. A fibrous hyperplasia is also present. The vessels throughout the cord show definite sclerosis (Fig. 9).

The medulla shows no changes aside from slight meningeal infil-

FIG. 6.—Thoracic cord, showing almost complete posterior column degeneration with some distortion of the cord. (Weigert.)

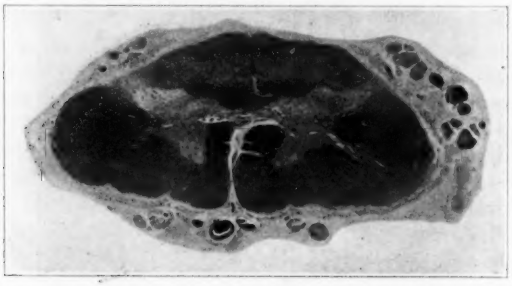

FIG. 7.—Thoracic cord, showing same as Fig. 6, with distortion of anterior horns.

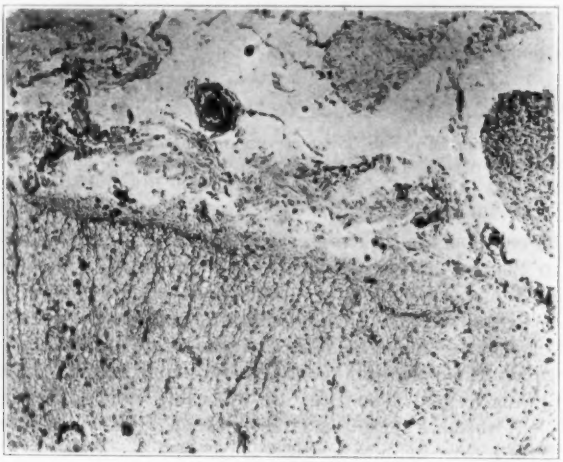

FIG. 8 —Pia-arachnoid, showing round-cell infiltration. × 115. Toluidin blue stain.

tration and sclerosis of its vessels. Unfortunately the peripheral nerves and muscles were not removed nor were the intestines very carefully examined.

Pathological Diagnosis. Meningomyelitis (syphilitic type).

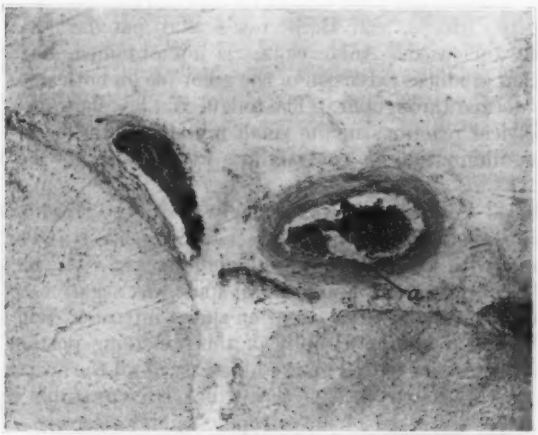

FIG. 9.—Anterior spinal artery cervical cord, showing endarteritis with splitting of elastic lamina (*a*). × 115. H. and E. stain.

CASE V.—A white widow, aged fifty-five years, came to the neurological dispensary of the hospital of the University of Pennsylvania on March 6, 1923. Her chief complaint was weakness of the left arm and hand.

The patient was married for ten years when her husband died. She had one stillborn child. No other pregnancies. She denies the use of alcohol.

We are able to report this case through the kindness of Dr. William G. Spiller.

Present Illness. About nine months ago the woman noticed weakness of her left hand; she first observed this because she frequently dropped articles from her hand. The weakness gradually progressed, until at the end of two months she was unable to use her hand to any extent. About this time she noticed that the hand was becoming smaller. She has had not pain although at times she has a jumping sensation in her arm. She has no trouble with her eyesight, and no sphincter disturbance. Her right hand has not been affected although she says it has a queer feeling.

Physical Examination. The pupils are equal, regular and react well to light and in accommodation. Examination of the eye-grounds shows that the media is clear, the discs round, and of fair color and

good outline. The vessels show moderate sclerosis and there is no fundus lesions.

The left hand is markedly atrophic and is in the claw position. The muscles of the forearm, arm, and especially of the shoulder girdle, are somewhat atrophic. The muscle power of the left upper extremity is much less than that of its fellow, which is about normal. The biceps, triceps, von Bechterew's and patellar reflexes are bilaterally increased. Ankle clonus is not obtained, but plantar stimulation produces extension of the great toe on both sides. Sensation is normal throughout. The tongue and lips show no atrophy. The electrical reactions in the small muscles of the hand show a moderate diminution in contractility in response to the faradic current.

The blood Wassermann was strongly positive. Examination of the cerebrospinal fluid showed a negative Wassermann and colloidal-gold curve, with two cells to the cubic millimeter. The roentgenogram of the cervical and upper dorsal spine was negative.

This case of nine months' duration shows intense atrophy of the left hand and moderate atrophy of the remaining portion of the left upper extremity with a marked increase of all the deep reflexes, and a bilateral Babinski, a picture which is comparable in every way to an early stage of amyotrophic lateral sclerosis. With a strongly positive reaction of the blood we believe we are justified in considering this case one of spinal syphilis involving the anterior horns and the lateral tracts.

Since the time when, in 1893, Raymond definitely established a relationship between syphilis and progressive muscular atrophy, by a description of a diffuse meningomyelitis, vascular in origin—and since 1905, when Dana suggested the probability of all spinal muscular atrophies being due to syphilis, and being a clinical form of spinal syphilis, with predilection for the anterior horns, just as Erb's spastic paraplegia is due principally to lesions of the lateral tracts and tabes dorsalis consequent principally upon an involvement of the posterior roots, until today when Léri says "I believe that progressive spinal amyotrophia is always or almost always due to syphilis," how much has our teaching progressed in the way of stressing the importance of treating all such muscular atrophies as parasyphilitic conditions as we have learned to treat tabes dorsalis, thanks to the writings of Fournier in 1876 and of Erb in 1879?

Summary. The amyotrophic form of spinal syphilis is a syndrome actually due to syphilis of the anterior horns and may or may not be associated with a tabes dorsalis or paresis. The object of this paper is an endeavor to focus attention on this point, in the hope that, by the frequent reporting of many cases of spinal progressive muscular atrophy, when syphilis is found to be the cause, and in which postmortem findings demonstrate the syphilitic structural

changes, this knowledge will become so generalized that antiluetic treatment will be immediately instituted, just as it is today in tabes dorsalis and paresis.

Of course, any conclusions based on the findings in our own few cases would not be justified. The writers hope to collect data on a sufficient number of cases to warrant some definite conclusions, but take the present moment as an opportunity to awaken the interest of the profession in order that all available cases of this sort may be investigated and reported with postmortem findings, if possible, so that from the mass of data the truth may ultimately be known.

A STUDY OF THE BACTERIOLOGICAL FINDINGS IN THE LYON-MELTZER TEST.

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A proper understanding of the various factors influencing the bacteriology of the duodenal content has become essential with the introduction of the Lyon-Meltzer method in the study and treatment of the diseases of the biliary system.

For diagnostic purposes, the method briefly consists of the microscopical and bacteriological study of three samples of duodenal material obtained after the installation of magnesium sulphate in 25 to 30 per cent solution. These samples are supposed to be derived from the common duct, the gall-bladder and the hepatic ducts respectively. Admitting such origin, the question naturally arises as to the significance of the bacteriological findings in these samples, especially as to whether microörganisms so found, may be considered of pathological significance, or merely as unavoidable contaminations.

Recalling for the moment that into the duodenum is emptied the gastric chyme, the bile and pancreatic secretions, as well as the secretion of the duodenal mucosa, and at times, material from the small bowel, it would seem evident, that organisms obtained from the duodenal content might have their origin in either the mouth, stomach, biliary system, pancreas or small bowel.

Our present knowledge of the bacteriology of the upper alimentary tract is far from complete. It is well known that innumerable organisms of various types, having their origin in the nose, mouth, throat, lungs and food are constantly being swallowed. It is also rather generally accepted that the acid gastric juice effectually

destroys such swallowed organisms and that the duodenal content is normally sterile.

The work of Cushing and Livingood[1] partially confirms this opinion, as they concluded after careful surgical studies, that in the normal healthy adult, the stomach, duodenum and upper small bowel rapidly become amicrobic in the fasting state. However, they also state that during digestion, numerous organisms having their origin in the ingesta, successfully resist the action of the acid gastric juice, and may be recovered from the duodenum. In their studies, yeast and coccal forms appeared most frequently in the duodenal samples.

Other investigators have attempted studies of the duodenal content by means of the duodenal tube, but their results are less convincing. Thus Hess,[2] obtaining the samples by means of a small catheter passed into the duodenum of fifteen infants, found Bacillus coli once, but staphylococci frequently. Later, MacNeal and Chase[3] studied twenty-four adults, using a duodenal tube, the tip of which was protected by a salol coated gelatin capsule to prevent contamination during the passage of the tube. From this series, they concluded that normal duodenal fluid is practically free from living bacteria when food is absent, but that the number of cultivable microbes in the duodenal fluid is markedly increased in variously gastro-intestinal disturbances.

The question naturally arises as to whether samples obtained by the duodenal tube method can be properly compared with those obtained by direct surgical means, in other words, is the duodenum into which a duodenal tube has found its way, a normal fasting duodenum? There can be no question but that the passage of the tube stimulates a more profuse salivary secretion than is present in the normal fasting state, and that a large part of this secretion is swallowed with the tube and while the tube is in the duodenum.

Just what effect the tube has on gastric secretion and peristalis, may be open to question, but again, there is no doubt that periodically, gastric content is discharged into the duodenum while the duodenal tube is in place. It would therefore seem possible that the findings of Hess[2] and MacNeal and Chase[3] may have been influenced by salivary contamination, which was a less marked factor in the work of Cushing and Livingood.[1]

Ample proof is at hand of the very high bacterial content of saliva. Streptococci and staphylococci have been demonstrated in over 80 per cent of fifty-four samples from dyspeptic patients by Smithies. The work of Kopeloff[4] is of interest in this connection, as he studied the gastric flora during a fractional test-meal. He isolated thirty-two types of organisms from the gastric contents and almost invariably found the same organisms in the saliva and the material of the test-meal, the saliva furnishing the members of the streptococci and staphylococci groups, the test-meal, the remaining groups. He concludes that the bacterial flora of the stomach is almost entirely

dependent upon the saliva swallowed, and also that the degree of acidity plays no appreciable role in determining the type of organism found.

Granting then, the presence of organisms in the stomach, practically all investigators agree that, even with normal acidity, there is abundant opportunity for them to pass unharmed into the duodenum.

With this evidence, we may conclude that although the normal fasting duodenum may rapidly become amicrobic when examined directly, there is no satisfactory evidence that the duodenum of the gastro-intestinal patient is amicrobic when examined in the fasting state by means of the duodenal tube, whereas, on the contrary, there is evidence that the saliva carries an abundant bacterial flora to the stomach and that the gastric flora, to a very large extent, determines the duodenal flora.

The possibility of such contamination of the biliary samples has been more or less clearly recognized by Lyon and some of his followers and two methods have been proposed to prevent it.

Whipple,[5] following the technic of MacNeal and Chase, used a tube, the tip of which was sealed with a salol coated gelatin capsule, which was not dissolved until the tip had reached the duodenum. By this means, it was thought that contamination with "organisms carried down in the effort to swallow the tube," was at least to some extent prevented. With this technic, he studied 150 cases and boldly concludes that "The colon bacillus, the hemolytic streptococcus and Staphylococcus aureus, especially if found in the bile following the magnesium sulphate, may be considered as etiological factors and as probably present in the gall-bladder or common duct or both." Recalling that he has not excluded salivary contamination, as the organisms carried down in the effort to swallow the tube may have gone on into the duodenum and contaminated his bile samples, these seem unjustifiable conclusions.

Lyon,[6] on the other hand, has attempted to sterilize the mouth and stomach by the use of permanganate and zinc chloride. The following quotation is of interest:

"To make possible accurate diagnosis of the duodenal biliary zone, it is necessary that we adopt means to prevent cytological and bacterial contamination from the mouth, teeth, tonsils, respiratory tract and stomach, from confusing us in our interpretations of duodenal and biliary materials.

"To avoid this as far as possible, I have adopted the following routine method in diagnosis: The patient presents himself with twelve-hour-fasting stomach, he then brushes his teeth carefully, rinses and gargles his mouth and throat thoroughly first with a strong solution of potassium permanganate gr. 1 to 1 ounce, then with a mild astringent solution of zinc chloride. Tube was freshly sterilized by boiling. The fasting content aspirated, is set aside

for chemical, cytological and bacteriological examination for comparison with the findings later recovered from the duodenum. The stomach is then rinsed to sparkling clearness, using gravity douching from 250 cc irrigating tanks or syringe douching and recovering the wash-water in 250 cc conical graduates in which can be noted how clean the stomach is—mucus, shreds, mucopurulent plugs and other material which yields much valuable information. After the wash-return is sparkling clear, the stomach is made astringent with Lavoris and then rewashed thoroughly. It is surprising to observe how often a stomach apparently washed clean, after being made astringent, will press out from the mucosal tubules mucopurulent masses, etc., often swarming with bacteria. After washing again, the stomach is disinfected with 250 cc of 1 to 10,000 permanganate solution immediately recovered, and stomach is again washed clear. This so far as possible, prevents contaminated material from the upper zones, confusing our interpretation of material later obtained from the duodenal biliary zone."

How far do such methods prevent contamination and make possible accurate diagnosis of the duodenal biliary zone? I believe the first method may be dismissed as unsatisfactory, as it is based on the assumption that the organisms found in the duodenum have their origin there, and neglects the contamination of duodenal content occurring with each discharge of gastric content.

The Lyon technic should be of value if it will do that for which it is designed, namely, the sterilization of the mouth, or better, the saliva, for a period of one to three hours, and secondly, the sterilization of the stomach, for an equal period.

As regards sterilization of the saliva, one can readily demonstrate that this is impossible by the method proposed by Lyon. Numerous tests were made on healthy members of the staff—taking cultures of the saliva before applying the Lyon method of treating the mouth, and at half-hour intervals after such treatment, over a period of two hours. In every case, the tubes, after attempted sterilization, were practically indistinguishable from those before, all showing most profuse growths. As it was thus evident that infected saliva was entering the stomach during the course of the routine test, no effort was made to determine the effect of the Lyon method of attempted sterilization of the stomach. In this connection, one statement of Lyon however, is of interest: "It is surprising to observe how often a stomach, apparently washed clean, after being made astringent, will press out from the mucosal tubules, mucopurulent masses, etc., often swarming with bacteria." If such plugs are pressed out by the astringent action of Lavoris solution, it seems probable that other similar plugs are pressed out by peristalsis during the fifteen minutes to two hours consumed by the test.

It seemed perfectly evident that the infected saliva swallowed

during the course of the routine test, eventually finds its way into the duodenum, but to demonstrate that such was the case, we have repeatedly placed a few grains of powdered charcoal on the tongue of patients undergoing the examination, and almost without exception, particles of charcoal have been recognized either macroscopically or microscopically in the bile samples before and after the administration of the magnesium sulphate.

From the foregoing, it is apparent that even with the Lyon technic, infected saliva is being swallowed during the course of the examination, that the organisms thus swallowed are not destroyed by the gastric juice, but are passed on into the duodenum where they may contaminate the various bile samples and render reliable bacteriological conclusions impossible. To investigate this assumption, a series of cases was examined, cultures being made from the pharynx, the fasting gastric content, the fasting duodenal content and the so-called *A*, *B* and *C* bile samples.

Our routine, because of the demonstrated impossibility of sterilizing the mouth, was less elaborate than that proposed by Lyon. Patients presented themselves at eight o'clock in the fasting state and a swab was taken from the tonsil areas, the mouth was then thoroughly rinsed with a 1 to 5000 permanganate solution. A freshly sterilized duodenal tube was then swallowed and the gastric content extracted and a culture made. The stomach was then thoroughly rinsed with a 1 to 10,000 permanganate solution until the washings returned clear. When the tube was apparently in the duodenum, its position was confirmed by fluoroscopical examination, after which, a culture of the duodenal content was made. Sterile mangnesium sulphate was then administered and the various samples of bile collected and cultured.

TABLE I.

Source of material.	Cultures, positive.	Cultures, negative.	Specimen not obtained.	Cultures similar to those of:								Cultures unlike.			
				Pharynx.		Stomach.		Duodenum.		"B" bile.		Pharynx and stomach.		Pharynx stomach, duodenum.	
				No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.
Pharynx	56														
Fasting gastric content	30	16	10	16	53										
Fasting duodenal content	29	17	10	20	69	13	45	..	..	..	..	5	17		
"B" bile	35	15	6	20	57	16	45	19	54	..	..	5	14	2	5
"C" bile	26	18	12	12	46	11	42	12	48	24	92	7	26	2	8

We had for comparison, 56 cases so studied. By referring to Table I, it will be seen that the fasting content, duodenal content,

B bile and *C* bile gave growths similar to that obtained from the mouth in from 46 per cent to 69 per cent of the cases and that the various bile samples gave cultures resembling those of either mouth or stomach in from 74 per cent to 86 per cent of the cases. In other words, in only 14 to 26 per cent of the bile cultures, was there an absence of organisms similar to those found in the mouth and stomach. It is probable that there would have been a closer agreement between the mouth cultures and those of the fasting gastric content, if cultures had been taken from the saliva, rather than by swabbing the tonsil areas. The various types of staphylococci and streptococci were the organisms most frequently found.

Conclusions. With these findings, it seemed apparent to us that no reliance could be placed on the bacteriological findings in the various bile samples and that even with the most painstaking technic, including the study of the mouth and gastric flora, the procedure is bacteriologically so fundamentally faulty that its use in the routine clinical study of the "duodenal biliary zone" is apt to lead to more incorrect than correct conclusions.

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THE VALUE OF PHYSICAL SIGNS IN THE EARLY DETECTION OF PULMONARY METASTASES.

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The Need for the Early Recognition of Metastases of Malignant New Growths. The early recognition of metastases to the lungs or pleura in those types of malignant tumors in which such metastases are prone to occur is of fundamental importance. For the purposes of this paper it was considered advisable to select two typical examples of such cases; namely, mammary carcinoma and osteogenic sarcoma. Careful physical examination of the chest should form a part of the general survey which a patient suffering from either of these diseases undergoes when first seen. The recognition of metastases at this time has an important bearing both on prognosis and

on the kind of treatment to be carried out. There is no doubt that many breasts have been needlessly amputated and many limbs sacrificed in cases complicated by unrecognized metastases to the lungs or elsewhere at the time of operation. By the early discovery of such metastases not only could these patients be spared an unnecessary operation, but in certain selected cases better palliation could be obtained by the use of radiation, and at the same time additional material would thus be made available for the study of the effect of various kinds of radiation on the various types of these two diseases. There is believed to be some evidence that the operative removal of a primary malignant growth imparts increased growth stimulus to metastases, so that the operation, in such cases, not only does no permanent good, but may actually shorten the life of the patient; while with proper selection of patients, it is possible that a certain number of cases of mammary carcinoma or osteogenic sarcoma with early secondary tumors in the lungs might be benefited temporarily by radiation. To be sure, it seems advisable, at times, to amputate a foul, ulcerating, painful breast or a large painful osteogenic sarcoma, even in the presence of metastases, without any hope of curing, but as the best means of speedy palliation.

Comparison with Pulmonary Tuberculosis. In the examination of cases of pulmonary tuberculosis, it is now generally accepted that reliance cannot be placed entirely on the radiographic plate or film for the detection of incipient cases. In a certain proportion, small, to be sure, but nevertheless well established, the physical signs in conjunction with the anamnesis and other findings, prove the presence of tuberculosis in cases in which the roentgenologist is unable to confirm the diagnosis. On the other hand the clinician is sometimes greatly surprised to find evidence on the roentgen-ray plate of well-marked tuberculosis which he had not suspected, or which he may have suspected from other data, but of which he had been unable to elicit any physical signs. The same situation exists, I think, in pulmonary metastases, especially in mammary carcinoma. Just as in pulmonary tuberculosis, there is, on the whole, close correspondence between the radiographic or fluoroscopical signs and the physical signs; but there are some cases in which the clinician is considerably surprised at the extent of metastatic involvement visualized by means of the roentgen-ray, and I think there is a certain small number of cases in which physical signs of metastases can be elicited before the lesions are of sufficient size or density to cast a distinctive shadow on the plate. The clinician should therefore avail himself of both methods of examination. The examination of the chest will often furnish the indication for taking a roentgen-ray picture, to confirm the presence of metastases and to reveal more accurately perhaps their size, character and location.

Metastases of Breast Carcinoma to Lungs and Pleura. Among the early symptoms which lead one to suspect metastases to the lungs are cough, vague or pleuritic pains in the chest and a feeling of difficulty in getting the breath.

The earliest sign which I have observed is a peculiar limitation of breath sounds, especially marked during inspiration, covering a limited area of the chest. This may or may not be accompanied by fine crackling rales during inspiration, and there may be no dyspnea, no cyanosis, no change in percussion note or fremitus, and no alteration in the vesicular quality of the breath sounds. This limitation of breath sounds, and particularly during inspiration, gives the impression that there is either something preventing normal expansion of lung vesicles, or a thin layer of something obscuring the vesicular murmur. The above signs may be the only ones obtainable and at this stage, the roentgenologist may be entirely unable to confirm the clinician's suspicion of metastases.

In consulting the standard text-books of physical diagnosis one is struck by the fact that almost the only descriptions of physical signs in such cases pertain to well-advanced lesions.

It is important, of course, to rule out other lung conditions, such as the residuum of an old pneumonia or pleurisy, a beginning dry pleurisy and tuberculosis. If any of these conditions are present the difficulties of physical diagnosis (and of roentgenological interpretation as well) are considerably increased. In the absence of a history of pneumonia, pleurisy or tuberculosis, and in the absence of the acute pain usually accompanying a beginning pleurisy, if one has the signs described above in the lower half of the chest, one is much more inclined to suspect metastases than if the same signs were present somewhere in the upper half of the chest, where tuberculosis might be the more probable cause. The signs of metastases are more frequently discovered in the lower half posteriorly than at the apex or anteriorly, because at the apex it is difficult to rule out tuberculosis, and anteriorly the presence of the female breast often obscures the examination of the lung.

Later Signs. With advance of the secondary growths the signs become more marked and more diffuse, so that similar changes may affect a large part of one or both lungs. In addition to the crackling rales, sibilant or sonorous rales may be heard. Later, change in the percussion note and possibly broncho-vesicular or bronchial breathing may be detected. The rales, as the metastases progress, usually increase in loudness and number. There may now be a visible limitation of expansion of the lower thoracic walls (without fluid). Later, pleural effusion may occur and add its characteristic signs to those already mentioned. Dyspnea increases and cyanosis may be marked. The patient may have distressing cough with little or no sputum. Hemoptysis may occur.

Pleural effusion may occur much earlier and may then obscure

all other signs. It may in this way be a source of great diagnostic uncertainty, both to physical examination and the roentgen-ray, particularly in the very late metastases which sometimes occur years after an amputation of the breast. We have found little help in such cases from an examination of the fluid for tumor cells.

In the cases that have recently had an amputation of the breast, and in which one hears when listening over the chest wall at the site of the missing breast a number of crackling rales, it is very difficult to say whether one is dealing with an early pleural metastasis or with a postoperative pleuritis. It is my impression that there is frequently a slight postoperative pleuritis directly beneath the operative field which gives rise to crackling rales that sound as though they were close to the ear.

Metastases to Lungs from Osteogenic Sarcoma. The lungs are almost invariably sooner or later the seat of metastases in this disease. These secondary growths start from cell emboli transported through the blood stream, while in breast carcinoma the route of dissemination is chiefly the lymphatics. As seen on the roentgen-ray plate, they first appear as small round, fairly clean-cut nodules lying within the lung. The symptoms are cough, pain in the chest, and later dyspnea and frequently hemoptysis. These growths when first seen on the roentgen-ray plate may be so small or lying so deeply within the lung parenchyma that no physical signs whatsoever can be obtained, and in these cases reliance for the first detection of metastases, it seems, must be placed on the roentgenological examination, whereas in the case of breast carcinoma metastases the signs may appear before the roentgen-ray findings. It should be borne clearly in mind, however, that these lesions do not become visible on the roentgen-ray plate from the moment of their inception, and that when cough, dyspnea, pain in the chest, hemoptysis or any combination of these symptoms occurs that cannot readily be accounted for by some other lesion, metastases should be suspected even in the absence of physical signs or roentgenological evidence of pulmonary newgrowth.

Later Signs of Metastases of Osteogenic Sarcoma. Later, as the nodules increase in bulk, one obtains various signs, dullness to flatness over some area with crackling and possibly sibilant rales, decreased breath sounds of relatively normal quality or breath sounds changed toward bronchial type. Massive growths may occur which practically obliterate all resonance, breath sounds, fremitus and voice sounds over an entire side or over most of the chest, even in the absence of sufficient fluid to produce such signs. Bulging of a portion of the chest over a massive growth may occur. Retraction of a portion of the chest wall over a secondary lung tumor, which is said to occur sometimes, according to several writers on physical diagnosis, I have never observed. Pleural effusion frequently occurs in these cases, also, and may occur early, so as to mask other signs, both physical and roentgenological.

Mammary Carcinoma: Comparison of Physical Signs with Roentgen-ray Findings. Following is a table comparing physical findings in the chest with roentgen-ray reports in cases of mammary carcinoma. The table includes all of the cases examined personally by the writer from the middle of August, 1920, until about May 1, 1923, with the exception of a good many cases which had to be excluded because of failure to secure the physical examination and the roentgen-ray plate at the same time. There are 216 cases included, of which 7 were men. In all cases the chest examination was made first as part of the routine physical survey, and the roentgen-ray plate was taken later on the same day or within a very few days thereafter. The roentgen-ray plates have been interpreted by Dr. R. E. Herendeen, roentgenologist to the hospital, independently, without any knowledge of the writer's findings. All of these cases have been definitely classified by the breast department as cases of mammary carcinoma clinically, confirmed whenever possible by pathological examination.

TABLE COMPARING PHYSICAL SIGNS WITH ROENTGEN-RAY FINDINGS IN CASES OF MAMMARY CARCINOMA EXAMINED FOR PULMONARY METASTASES.

	Number of cases.	Per cent.
GROUP I.—Physical Signs Indicated Metastases:		
Confirmed by roentgen-ray	18	54.5
Roentgen-ray negative at first; later positive	2	6.1
Roentgen-ray questionable or suspicious	7	21.2
Roentgen-ray negative for metastases	6	18.2
Total	33	100.0
GROUP II.—Physical Examination Questionable or Suspicious of Metastases:		
Roentgen-ray positive for metastases	6	12.3
Roentgen-ray questionable or suspicious	13	26.5
Roentgen-ray negative at first; later positive	4	8.2
Roentgen-ray negative for metastases	26	53.0
Total	49	100.0
GROUP III.—Physical Signs Negative for Metastases:		
Roentgen-ray negative for metastases	107	80.0
Roentgen-ray questionable or suspicious	18	10.4
Roentgen-ray positive for metastases	9	9.6
Total	134	100.0
Grand total	216	

Discussion. In Group I there are 2 cases in which the physical signs were considered positive for metastases, and which were negative to the roentgen-ray at first, but which later showed definite metastases on the plates.

The first of these was patient Mrs. L. L., examined on December 27, 1920, and classified as recurrent inoperable. Her left breast had

been removed three years before and she had received four roentgen-ray treatments two years previously and four or five roentgen-ray treatments the preceding year, the last treatment having been given in September, 1919. The roentgen-ray plate on December 27, 1920, was reported as follows: "Plate does not reveal definite evidence of involvement of pleura, and there is no well-marked evidence of carcinoma metastasis to lungs. The left margin of the gladiolus sterni from second to third ribs seems hazy and irregular and lacking in normal bone density." A biopsy made at this time showed scirrhous carcinoma. On July 19, 1921, seven months later, the roentgen-ray showed "evidence suggesting metastases to lungs," and on September 24, 1921, "characteristic roentgen evidence of carcinoma metastases to lungs." On January 8, 1923, her liver was found to be greatly enlarged, and she died on February 12, 1923.

The second of these cases, Mrs. L. Gl., was examined on July 25, 1921, and classified as recurrent inoperable. The physical examination of the chest indicated the presence of metastases, but the roentgen-ray report was negative. Three months later, on November 1, 1921, the roentgen-ray findings were questionable or suspicious, and eight months later, on March 17, 1922, the roentgen-ray report was positive for metastases. On August 10, 1922, she was found to have a greatly enlarged liver, and she died on November 30, 1922.

Of the cases in Group II, suspected of having metastases as the result of physical examination, 4 were at first reported negative to the roentgen-ray, but later showed positive evidence of metastases on the plates, at intervals of from three and one-half to eight months after the original examination had been made. Three of these cases died in from five to ten months after first coming to the hospital. In one of these cases the only sign demonstrable at the first examination was a diminution of breath sounds at the right base. The remaining case of the four was last seen on March 20, 1923, seven and two-thirds months after her first examination, and was then in good general condition.

The 6 cases just discussed may be regarded as furnishing some evidence, but not proof, that the physical examination detected signs of metastasis of mammary cancer before it could be found on the roentgen-ray plate. It is impossible, of course, to prove that the metastases were present at the time when the physical examination was reported as positive or suspicious, and that they did not develop during the interval of time which elapsed before positive evidence was obtained on the plates; but inasmuch as the signs reported in the beginning in these cases are those found in other cases of known metastases, it seems reasonable to assume that changes were present sufficient to produce physical signs, but not sufficiently marked to cast a distinctive shadow on the plates.

Cases in Group I, reported as positive for metastases to physical

signs, in which the roentgen-ray was negative, numbered 6. Of these 3 died, eight months, one year, and fourteen months, respectively, after the first examination. No further roentgen-ray plates had been made. The patient who lived fourteen months was reported by the Social Service Department eight months after the first examination as coughing a great deal. One other patient is probably dead, as she was sent to a home for hopeless cancer cases in September, 1922. She presented an inoperable recurrence. No further plates had been made in this case. The two other cases have been lost track of. Both, however, presented inoperable recurrences. In one of these it seems almost certain that the roentgen-ray failed to show metastases which were present and indicated by physical signs. She first presented herself for examination on October 28, 1921 (Case B. W.). There was no history of any previous lung condition. An inoperable recurrence was present. The physical signs were reported as follows: "Dullness and diminished breath sounds in right axilla and at right base posteriorly. Fine crepitant rales at right base posteriorly. Undoubtedly metastases to pleura or lung." The roentgen-ray report was negative. This has been verified by reinspection of the plate. A biopsy was reported by Dr. James Ewing as carcinoma simplex. The case progressed rapidly, the opposite breast becoming involved. The patient, unfortunately, moved to Massachusetts in May, 1922, and cannot be traced.

Cases in Group II, reported as suspected of having metastases in which the roentgen-ray report was negative numbered 26. Of these 7 died in from three to nine months after their first examination at this hospital. All but 1 of these were classed as inoperable. Three other cases were lost track of so long ago that they are probably dead, and 2 cases were doing badly when last seen, making a total of 12 out of the 26 who are dead, about to die, or probably dead. Two others have been lost track of in the past year. The remaining 12 cases may be said to be in fairly good condition. Unfortunately later roentgen-ray plates of the lungs were made in only 2 of the 26 cases. In each of these the later roentgen-ray report was questionable or suspicious of metastasis. Both cases are living, but probably will soon die, as they were originally classed as inoperable twenty and thirty-one months ago, respectively.

Cases in Group I, in which the physical examination indicated metastases, and in which this diagnosis was confirmed by the roentgen-ray, numbered 18. Further confirmation of the physical examination is given by the fact that 12 of these died in from forty-two days to twenty-one months afterward, several of them having severe cough, dyspnea, pleural effusions and so forth. In 9 of these the record definitely shows that death was due to extension of the carcinoma, with pulmonary, bone or liver metastases. One other case (E. S.) has not been seen since January 31, 1923. She had five later plates made of the chest, which showed definite evidence

of progression in the pulmonary metastases. Case A. P., last seen in September, 1922, complained of pain in her knees, but the roentgen-ray plate was negative for bone involvement. Case H. T., last seen in September, 1922, complained of generalized pains. Case C. L., last seen May 28, 1923, was in poor general condition. Thus, only 2 cases remain out of the 18 who are in good condition. One of these presented an unusual type of breast carcinoma, there being a history of a breast tumor of twenty-five years' duration. Furthermore, only five months have elapsed since these 2 cases first presented themselves for examination.

Cases in Group I, in which the physical signs indicated metastases to the lungs, and in which the roentgen-ray report was questionable or suspicious, numbered 7. Of these 4 died in from three to ten months after their first examination. Of the 3 cases presumably alive, 2 were inoperable, and all 3 have been recently ill with pains suggesting bone metastases. Further plates of the chest had not been made in these cases.

Of the cases in Group II, in which the physical examination was questionable or suspicious of lung metastases, the roentgen-ray report was positive in 6. Of these, 3 died in from nine to ten and one-half months. Of the remaining 3, one, a man, presented an inoperable recurrence, has not been heard from since October, 1922, and is probably dead; another inoperable recurrent case has not been seen since June, 1922, and is probably dead. In the latter case later roentgen-ray plates confirmed the presence of lung metastases, incidentally showing some improvement following high voltage roentgen-ray therapy. The remaining case presented a primary inoperable carcinoma, and is apparently in fairly good general condition at present, seven months after her first visit to the clinic.

Of the cases in Group II, regarded as suspicious for pulmonary metastases from the physical examination, the roentgen-ray report was also suspicious or doubtful in 13. Four of these patients died in from fifty-one days to eleven months after their first visit. Of the remaining 9 cases, 1 is probably dead, 3 have been lost track of, 1 is doing badly, 2 have shown positive evidence of pulmonary metastases on chest plates made five and seven months, respectively, after the initial examination, 1 case showed no change on a plate made three months after her first visit, and only 3 cases are known to be in good general condition.

Contrast with Cases Negative to Physical Examination. The preceding 82 cases were all regarded as positive or suspicious for pulmonary metastases as a result of physical signs obtained, and by their roentgen-ray plates or subsequent course tended to bear out the accuracy of the physical findings in varying degrees. With these I wish to contrast the following 134 cases which were reported as negative for evidence of pulmonary metastasis on physical examination.

The roentgen-ray confirmed this negative report in 107, or 80 per cent. Of these 107 cases, only 31 are recorded as dead or "final" (the term "final" indicating that the case has been lost track of and not necessarily that it is dead). In 15 cases, later roentgen-ray plates, made after an interval of seventeen days to twenty-two months after the first plates, have also been negative. It should be reëmphasized at this point that all the cases included in this report have been definitely classified as cases of mammary carcinoma by the breast service. Three cases showed questionable evidence of lung metastases on roentgen-ray plates made from one to six months after the original negative plates, and 7 of the 107 showed positive evidence of pulmonary metastases on later plates made from two to eight and one-half months afterward. However, in 1 of these cases (A. N.) an opportunity was afforded the writer to examine the chest the day before the roentgen-ray picture was taken, and physical signs of metastases were found and formed the principal reason for having a roentgen-ray plate made.

Of the cases regarded as negative for pulmonary metastases on physical examination, the roentgen-ray reported questionable evidence of metastases in 18 cases, or only 10.4 per cent. Eight of these are dead and 3 others are probably dead. Three showed definitely positive evidence of metastases to the lungs on plates made two to eight months later. Three others were still questionable to the roentgen-ray ten to twenty-three months later, and 2 cases showed less definite evidence to the roentgen-ray three and seventeen months, respectively, after the original questionable plate. Later plates were not made in the other cases of this group.

Of the cases reported as negative to physical examination, with respect to pulmonary involvement, the roentgen-ray report was definitely positive for metastases in only 9 cases in all, or 9.6 per cent of the whole group of cases (Group III) negative to physical examination. Two of these are dead as a result of progress of the disease, 1 has not been heard from since August, 1922, when she was having some pain, and 6 are still in apparently good general condition. Later plates of 3 of the 9 cases (one now dead) confirmed the original roentgen-ray report. An excuse for failing to elicit physical signs in one of these cases may lie in the fact that on the roentgen-ray plate the shadows of the metastases were small, round, discrete, dense areas resembling sarcoma metastases, a quite different picture from the usual appearance of pulmonary metastases of mammary carcinoma. As will be shown below, physical signs of this type of secondary growth are much less readily elicited. This case may possibly represent an instance in which dissemination of mammary cancer took place chiefly through the blood stream, as in sarcoma, rather than through the lymphatics.

Following is a table comparing the findings on physical examination of the chest with the roentgen-ray reports in cases of osteogenic sarcoma. These cases were all examined by the writer between

August, 1920, and May, 1923. Almost an equal number had to be excluded because for one reason or another the physical examination and roentgen-ray examination were not made near enough together for the purposes of this study:

TABLE COMPARING PHYSICAL SIGNS WITH ROENTGEN-RAY FINDINGS IN CASES OF OSTEOGENIC SARCOMA EXAMINED FOR PULMONARY METASTASES.

	Number of cases.	Per cent.
GROUP I.—Physical Examination Indicated Metastases:		
Confirmed by roentgen-ray	2	100.0
Total	2	100.0
GROUP II.—Physical Examination Questionable or Suspicious for Metastases:		
Roentgen-ray negative for metastases	1	
Total	1	
GROUP III.—Physical Examination Negative for Metastases:		
Confirmed by roentgen-ray (negative)	9	75.0
Roentgen-ray positive for metastases	2	16.6
Roentgen-ray positive twenty-one days later	1	8.3
Total	12	100.0
Grand total	15	

Discussion. GROUP I. That the physical examination and roentgen-ray were correct in indicating pulmonary metastases is confirmed in one of these 2 cases by the fact that he lived only forty-eight days after the first examination. The other case disappeared after seven days, but the physical signs and roentgen-ray evidence indicated a large mass in the upper right lobe, and as he has not been seen since August, 1922, it is probably safe to assume that he is dead.

GROUP II. In the single case of this group, three subsequent plates of the chest taken one, two and three months, respectively, after the first examination were also negative. Moreover, a second physical examination of the chest made five days before the last plate was made was also negative; so that the second examination of this case might be added to the following group (Group III) as a negative case confirmed by roentgen-ray. She died five months after the first examination.

GROUP III. Cases negative to physical signs and confirmed by the roentgen-ray numbered 9, or 75 per cent of this group, to which might be added the second physical examination of the single case in Group II, so as to make 10 out of 13 cases confirmed by roentgen-ray, or 76.9 per cent. Of the 9 cases, 7 had later plates made; 5 remained negative to the roentgen-ray for periods of three to fourteen months; of these, 2 died after six months, 2 were lost track of after four and a half and fourteen months of observation.

and 1 is still living after fourteen months, but has recently developed a questionable metatarsal metastasis. One of the 7 cases had a questionable plate four months after the initial examination, and died after eight months and 1 case showed positive evidence of pulmonary metastases after an interval of six months. In this case it is of interest to note that plates made only one and two months previously had been negative. A plate made a month later showed progress of the secondary growths. This patient died after seven and two-thirds months. Of the 2 cases in this group who did not have later plates made, 1 died after four months and 1 was lost track of after six and one-half months, but was then apparently in fair general condition.

In Group III, 2 cases were reported as showing pulmonary metastases on the roentgen-ray plate whose physical examination had been negative. In one of these, a second plate made four months later was negative. Whether this represents a result of treatment, or a spontaneous regression of the tumor, it is not within the province of this paper to discuss. This case was still alive on March 1, 1923, two years and four months after the first examination. The other case had a second plate made after four months, which showed an increase in the secondary tumors. Radiographs of his chest which had been made at Bellevue Hospital had been reported as follows: Negative five months before admission to the Memorial Hospital; positive for metastases four months before admission. He was lost track of in May, 1922.

Case I. S. of Group III, whose last roentgen-ray plate had been negative and who died three months later, was autopsied. Following are the findings pertaining to the chest: "Both lungs are the seat of many marble-sized, well-circumscribed, whitish, sometimes ossified tumors. Opposite the lower dorsal vertebra on the left side is an extrapleural partly ossified metastatic tumor 3 cm. in diameter, about which is a localized pocket of pus 2 cm. in diameter."

Case J. R. of Group III, whose roentgen-ray plate was positive twenty-one days after the physical examination had been reported negative for metastases, also came to autopsy. "On opening the chest, the anterior mediastinum is found filled with moderately hard tumor masses which are densely adherent to the sternum. The pericardium contains a slightly increased amount of fluid. In removing the heart, tumor masses are found attached to the lung side of the pericardium, and at the base of the heart, infiltrating the pericardium in the region of the openings for the large vessels. Both pleural cavities contained about 500 cc of clear fluid. The left lung was adherent at several points, especially at the apex and base, and infiltrated by masses 1 to 10 cm. in diameter. There were 15 to 20 of these which were attached to diaphragm as well as pleura, and some were quite firmly adherent to ribs. The right

lung was almost entirely replaced by tumor masses 1 to 15 cm. adherent to parietal pleura, ribs, and diaphragm." There were metastases also to posterior mediastinum, liver, kidneys and retroperitoneum.

Summary. 1. It is essential to search carefully for the presence of metastases before planning the treatment of malignant neoplasms.

2. In this paper are described the physical signs of early as well as late stages of metastasis to lungs and pleura in two typical types of malignant neoplasms in which such secondary growths frequently occur: mammary carcinoma serving as an example of carcinoma and osteogenic sarcoma as an example of sarcoma. There are 216 cases of carcinoma of the breast and 15 cases of osteogenic sarcoma reported in the form of tabulated comparisons of the results of physical examination and roentgen-ray examination of the chest for metastases.

3. The earliest physical sign of metastasis to pleura or lung from breast carcinoma is a patchy limitation of breath sounds, particularly during inspiration. This sign may or may not be accompanied by crackling rales or pleural friction rubs. It may be detected in some instances before the roentgenologist is able to demonstrate any shadow distinctive of metastasis. The later signs correspond to those described in text-books of physical diagnosis.

4. The earliest demonstrable physical signs of chest metastases of osteogenic sarcoma may not appear until some time after the roentgen-ray has succeeded in showing the small, round, well circumscribed nodules.

5. A tabulated comparison of the results of physical examination and roentgen-ray findings shows a fairly close agreement. For example, in breast carcinoma, of 33 cases considered positive for chest metastases as a result of physical signs, 27 or 81.8 per cent were to the roentgen-ray either positive at once, positive after an interval, or questionable or suspicious, and only 18.2 per cent were frankly negative to the roentgen-ray.

Of 49 cases which were questionable to physical signs, 23 or 47 per cent were either positive at once to the roentgen-ray, positive after an interval, or questionable, while 26 or 53 per cent were negative.

Of 134 cases considered negative to physical signs, 107 or 80 per cent were negative to the roentgen-ray, 18 or 10.4 per cent questionable, and only 9 or 9.6 per cent frankly positive.

In the small number of cases (15) of bone sarcoma suitable for this study, a similar close agreement was found between physical signs in the chest and the roentgen-ray reports.

6. In cases of cancer of the breast and bone sarcoma, careful physical examination of the chest should always be made in addition to the roentgen-ray examination in order to disclose metastases to lungs or pleura as early as possible.

CHRONIC APPENDICITIS AND ITS DIFFERENTIAL DIAGNOSIS.*

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Whereas acute appendicitis is in the majority of cases easily diagnosed, chronic appendicitis offers such great difficulty that a detailed discussion of the differential diagnosis needs no apology. Ever since Fitz and Gaston over thirty years ago discovered the important rôle played by the pathological condition of the appendix, the subject has rightly received almost continuous attention.

Acute appendicitis is purely a surgical disease, so much so that the internist but seldom sees such cases at all. Chronic appendicitis, on the other hand, may still be considered a borderline disease, because the symptoms, as will be shown below, are so varied that the patient usually consults the internist long before he does the surgeon, and, because it leads to so many other intra-abdominal complications that even the removal of the appendix may not relieve the symptoms.

Anatomy. For a careful discussion of the differential diagnosis, a brief review of the anatomical peculiarities of the appendix and its pathology is necessary. Anatomically, the appendix presents a small, blind pouch attached to the tip of the cecum. It has the shape of a tube and lies freely in the abdominal cavity. By its vascular and lymphatic supply, as well as by the easy giving way of the walls of the appendix, in disease, and also by the fact that it may spread its noxious influence not only to the immediately neighboring viscera but also to the more distant parts of the body, the pathological appendix is an unusual menace. The length of the appendix varies from 5.5 cm. to the longest which was 28 cm., described by Sonnenburg. It is longer in young individuals than in those of later life. The inner lumen is connected with the cecum by a reduplication of the folds of mucous membrane known as the Gerlach valve. This is, in reality, not a valve at all, as correctly pointed out by Colley, as it contains no muscles and possesses no sphincter action. This so-called Gerlach valve does not prevent the passage of contents from the cecum into the appendix, nor does this structure open in a sphincter-like manner to allow cecal contents to pass into the appendix. Hence the name valve is not correct. Contents passing from the cecum into the appendix and from the appendix into the cecum meet with no hindrance, unless the position of the appendix in relation to the cecum is such that the communication of contents between the two organs is not possible, or unless the connection between the two organs is pathologically obliterated.

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Normally the passage of cecal contents into the cecum is quite rapid. Horn found that lycopodium seeds introduced into the colon by means of an enema reach the appendix within fifteen minutes.

Grigorjews was the first to demonstrate roentgenologically that the appendix has peristalsis of its own, and that, depending on its contraction and peristalsis, it changes its position and also its contents, so that normally the appendix will be found to change in contour and also that it is sometimes filled and sometimes empty. This is mentioned here because it is very important in the roentgenological study of the pathologic appendix.

As to whether the appendix is normally filled with fecal matter, opinions differ. Ribberts, in his well-known pathological studies, asserted that a normal appendix is always empty. Klebs, on the other hand, found the appendix filled with feces in 57 per cent of his autopsy material. Aschoff, who paid a great deal of attention to the histological studies of the normal and pathological appendix, came to the conclusion that in 62 per cent of cases the lumen of the normal appendix may contain feces.

Of even greater importance is the fact whether the filled appendix has pathological significance. The roentgenological studies of the appendix have demonstrated beyond doubt, that the normal appendix fills and empties, and also changes its position and contour. Only as the appendix becomes diseased and its elasticity and contractility as well as persistent activity diminish, does it become impossible for it to empty its contents and alter its shape and position. The presence of thick, dried fecal matter and fecal stones in the appendix is, according to the opinion of all pathologists, usually an indication of disease. Such substances may be present in the appendix because the organ has lost its contractile and peristaltic power as a result of inflammation, thereby rendering it unable to rid itself of the fecal contents before being dried out or until a fecal stone forms, as may be the case in acute appendicitis. The fecal material may accumulate in the appendix, become hardened, and form a fecalith, which, in turn, leads to chronic irritation of the appendix and inflammatory changes.

The arterial supply of the appendix is furnished by the ileocolic artery; the blood is carried from the appendix by the ileocolic vein; the latter empties into the mesenteric vein. This is important to remember because, in cases of appendicular disease, the infectious material is at times carried from the ileocolic vein into the mesenteric vein, and so reaches the liver, giving rise to dangerous consequences.

The lymphatics form a network in the submucosa through which they have direct connection with the lymphatic vessels of the mesentery and the peritoneum. They empty partially into the glands lying at the angulus ileocecalis and partially between the layers of the mesentery and its communicating glands. The lymphatic vessels pass from the ascending colon and ileum to the upper surface

of the liver and the ligament connecting it with the diaphragm, and so form a direct communication between the lymphatics of the appendix and of the subphrenic space. There is no lymphatic connection between the female generative organs and the appendix. Affections of the generative organs secondary to appendicitis do not result, as was previously thought via the lymphatics, but by direct extension.

The nerve supply of the appendix is derived from the sympathetic fibers of the mesenteric plexus. The numerous branches and nerves connecting with the nerve fibers of the gastro-intestinal tract explain the fact that the pains which are present in appendicitis may spread over all parts of the abdomen and make the diagnosis of the origin of the pains most difficult. It is of great importance to remember that at times the ileofemoral nerve also connects with the nerves supplying the appendix. This explains why the appendicular pains sometimes extend to the scrotum and to the right thigh.

From the histological standpoint, it is most interesting to note that the appendix has a rich supply of lymph follicles. The lymph follicles are connected with the large lymph vessels, by means of capillaries and the basilary sinus, discovered by Lockwood. From the intestinal lumen the lymph follicles are separated by a thin, epithelial layer which forms small lacunæ in the muscularis mucosa which are very readily destroyed if the appendix becomes infected. Aschoff, who described these lacunæ, found that the areas offer no resistance to the entrance of disease-producing factors and are responsible for the rapid destruction of the rest of the appendix in case of disease. As these lymph follicles are most numerous in the young, it explains the greater frequency of the disease in young people and also why it is more dangerous in early adult life. After twenty or thirty years of age the follicles diminish greatly in number.

The mucous membrane also undergoes atrophy after middle life and may at times disappear, leading to total or partial obliteration of the appendix. The narrowing or occlusion of the lumen, the result of complete atrophy of the mucous membrane of the appendix, is, in the great majority of cases, undoubtedly the result of a previous inflammation which has led to fibrous tissue formation and to complete degeneration of the mucous membrane. Aschoff found in a small number of cases that obliteration of the appendix and complete atrophy of the mucous membrane may exist, however, without any evidence of previously existing inflammation. He showed that before ten years of age the appendix is obliterated in about 66 per cent of cases; up to twenty years of age it is obliterated in 12 per cent; up to thirty years, 20 per cent; after forty years, 28 per-cent; after fifty years, 42 per cent; and after sixty years, 14 per cent.

The course of the appendix is usually somewhat curved and runs toward the small pelvis. It possesses its own mesentery, on account

of which it can change its position. The course and position of the appendix depend a great deal on the development of the tip of the cecum. If the cecum is more strongly developed anteriorly and on its outer side, the appendix originates from the median line in front or behind the entrance of the ileum into the cecum. As the course and development of the teniæ determine the form of the tip of the cecum, the position of the appendix depends, on the development of the teniæ, whether they lie below, in front, or behind the ileum. The appendix lies freely in the abdominal cavity and may change its position, lying at times more to the inner side, at times farther below, and at times even above the cecum. The appendix situated in the small pelvis is more exposed to infections and its intimate relation in this position with the intestinal coils makes the appendix dangerous to the intestines, the female generative organs, the urinary bladder and rectum in case of disease. However, in this position encapsulation of a suppurative appendix is more frequent than if it is situated in the ileocecal region, where it has a greater opportunity to rupture into the free peritoneal cavity. If the appendix lies laterally in front, behind, or below the cecum (laterocecalis, retrocecalis, or subcecalis), there is greater protection against the spread of a general peritonitis. Two conditions greatly influence the change in the position of the appendix, namely, the variable position of the cecum proper and the changes in the peritoneum in the region of the appendix. Even under normal conditions the position of the appendix changes depending upon whether it is empty or filled with soft fecal material, or distended with gas. If the appendix is empty it lies behind the small intestine, opposite the anterior superior spine of the ileum. If filled with fluid feces, it drops into the small pelvis. If distended with gas, it even reaches the anterior abdominal wall on a line with Poupart's ligament.

In case of disturbance in the lumen of the colon, and in its transportation of fecal material, the position of the appendix lying either more superficially in the abdomen or lower down in the pelvis, is naturally influenced much more, depending on whether the cecum is filled or empty. Anomalies of the colon and its mesenteric attachment produce dislocation of the appendix of more serious consequences. Such anomalies may be responsible for the abnormal attachment of the appendix. De Quervain showed that if the ascending colon is so situated that it is entirely crowded by the coils of the small intestine the appendix may be pushed behind the cecum (retroposition) or to the left side of the abdomen (sinistroposition), or to the extreme right of the colon (dextroposition). If the cecum is situated very low in the pelvis on account of an abnormally long mesocolon, the appendix may lie on the symphysis and press against the urinary bladder; if, on the other hand, on account of a short mesocolon, there is dystopia of the cecum, the appendix may lie

behind the kidney, or close behind, or over the liver. In rare cases, as pointed out by Troell, the ascending colon may be absent and the cecum may begin at the hepatic flexure, in which condition the appendix may be found overlying the transverse colon.

Lane's kink and Jackson's membrane influence the position of the appendix. Cecum mobile and ptosis of the transverse colon may also influence the position of the appendix. The various anomalies in the position of the appendix are mentioned here because they play a most important rôle in the causation of its disease and in the immediate and remote consequences.

The Relation of the Appendix to the Peritoneum. In the majority of cases both the cecum and appendix are covered by peritoneum. Very rarely it may lodge retrocecally during embryonic life and be covered by peritoneum only anteriorly. Folds of peritoneum spreading from the cecum to the ileum and from the ileum to the appendix and from the ileum to the peritoneum, may form pockets which serve to limit the mobility of the appendix as well as that of the cecum, and even cause strangulation of the appendix and the cecum. Such folds are not constant. The folds, further, may serve as a protective agent against the spreading of the infection from the appendix to the general peritoneum; on the other hand they may also serve as a bacterial nest.

Pathology and Etiology. The appendix has offered unusual opportunities for pathological study because it has been removed by surgeons during every possible stage. The pathological changes in the chronic appendix vary a great deal. The fact that the chronic appendix is the result of a previously existing acute attack is accepted without question today. Even S. Oberndorfer[1] who, in his excellent pathological studies of the appendix, was at first of the opinion that chronic appendicitis may be present without previous acute inflammation, has conceded the conclusions of Aschoff, that acute appendicitis precedes chronic appendicitis in every case. The reason why the history in so many cases does not reveal the previous acute attack is because, in a great majority of cases, the ordinary stomach ache during childhood was, in reality, as pointed out by H. C. Deaver[2] and Albu and Rotter,[3] acute nonsuppurative appendicitis, from which the patient recovered without operative interference.

As it is now definitely established that chronic appendicitis is never primary, the chronic pathological changes in the appendix depend upon the damage done to the appendix during the acute stage plus the repeated recurrent attacks resulting from the infectious agent lodging in the diseased appendix. In order, therefore, to appreciate the pathological changes that take place in the chronically diseased appendix, a few remarks are necessary about the changes in the acute stage which may lead to chronic changes. In many cases, during the acute attack only the superficial epithelium

of the distal part of the appendix is destroyed. The defect in the epithelium becomes covered with a fibrinous leukocytic exudate and the underlying mucosa and submucosa show fresh leukocytic infiltration.

Such an early stage can only be seen if the appendix is removed within a few hours after the attack. In some areas of the appendix the process may recede during an early stage, leaving no evidence of inflammation. Such are the very mildest cases. As a rule, however, the initial stage progresses into a more complicated one. The infection perforates into the grooves of the mucous membrane and then to the serous membrane of the appendix, where it forms a serous leukocytic exudate and later a fibrinous exudate. Such a stage is termed by Aschoff[4] "appendicitis phlegmonosa ulcerosa simplex." If this process begins to recede, the superficially destroyed mucous membrane, together with the adhesions of the folds of the mucous membrane, lead to stenosis and occasionally also to atresia, giving rise to the obliterated appendix. The healing of the serous covering of the appendix leads to adhesion of either the appendix to the ileum, cecum, or, depending on the spread of the adhesions and the position and length of the appendix, to even more distant organs (generative organs, urethra, liver, kidney, hepatic flexure, spleen, sigmoid, etc.).

True suppuration, to the point of abscess formation, may take place in the lumen of the appendix and reach the serosa, which, however, becomes so encapsulated by fibrous tissue that it does not give rise to the necessity of immediate surgical intervention but remains the source of chronic irritation. The other forms of termination of acute appendicitis, such as perforation and gangrene, need not be discussed here, as they indicate immediate surgical intervention. One of the other sources of chronic appendicular disease without gross changes in the appendix may be due to the fecal stone lodging in the appendix. The question, whether the fecal stone may exist in a normal appendix or be the result of an infection of the appendix, disabling it from ridding itself of the fluid fecal material and so causing fecal stone is also a matter of considerable discussion. Aschoff holds that fecal stone is usually superimposed upon an infection of the appendix and that it is associated with erosion of the epithelium and, in some cases, even with the destruction of mucous membrane and weakening of the musculature of the appendix. From the clinical standpoint it is important to remember that, although in some appendices the fecal stone may be found postmortem in cases where the history does not point to any appendicular disease, there is no doubt that the fecal stone is an indication of disturbed peristalsis in the appendix and that it is frequently the cause of appendicular colic.

The changes in the chronic appendix, therefore, may be stenosis, induration of the walls of the appendix, retention of mucus, fecal

masses and fecal stones and kinking by means of adhesions. All these changes necessarily give rise to a varied clinical picture. In addition to that, the mesentery of the appendix is also often contracted on account of adhesions which invade the nerves and give rise to considerable pain. The process may extend to the wall of the cecum, causing a moderately contracted and spastic cecum or it may cause catarrh of the mucous membrane of the cecum with dilatation, the so-called typhlatony. At times pathological changes in the appendix may be the cause of diverticuli. From the clinical standpoint it is very important to remember that the appendix may become secondarily invaded as a result of gall-bladder disease or generalized or localized colitis and infection of the female generative organs.

Rheindorf[5] expressed the opinion that a great many cases of chronic appendicitis are due to worms lodging in the appendix. Of course, a great number of cases in which worms were found in the appendix, have been recorded in literature by surgeons and pathologists, but very few are of the opinion that it is frequently a cause of chronic appendicitis. In this country worms are a very uncommon cause of disease, but there is no doubt that if worms lodge in the appendix, they may give rise to acute and even chronic appendicitis.

Cecil and Bulkley[6] described a characteristic form of appendicitis, due to parasites, which consists of catarrhal inflammation with small hemorrhages. The subjective symptoms are numerous, the objective symptoms meager. The disease is not rare. Wilson[7] states that thread worms are frequently the cause of chronic appendicitis and the reason why it is sometimes so difficult to cure thread worms by anthelmintics is because of those that lodge in the appendix.

Some authors have considered that in status lymphaticus the appendix is richer in lymph follicles and is longer and, hence, more frequently the seat of disease. That the appendix is in reality longer in individuals with status thymico-lymphaticus cannot be denied. It is due to the fact that these individuals are usually tall and thin and all the organs are longer and narrower, but that these are more likely to be afflicted with appendicitis than others is not proven. It is quite likely, however, that individuals of such status, if afflicted, are prone to have more symptoms as they are physically inferior and hypersensitive.

Tuberculosis, actinomycosis and carcinoma may affect the appendix without affecting other organs in the body. Actinomycosis, if it affects the appendix, is usually secondary to actinomycosis elsewhere in the body. It may also be stated that at times mucus cysts are found in the appendix and its mesentery. Such cysts have been named pseudomyoma. They may form a tumor of considerable size, or their gelatinous contents may break through the appendix into the peritoneum, or at times undergo malignant degeneration.

Maresch[8] found distinct neuromas in a number of obliterated

appendices which he attributes to the plexus of the submucosa becoming involved by fibrous tissue, which results in the process of healing of the ulceration in the mucous membrane of the appendix. Such neuromas may give rise to a great deal of pain and are, therefore, of clinical interest. It is analogous to the neuroma associated with ulcer of the stomach, to which Störck called attention.

Symptoms. The symptoms of chronic appendicitis may be so pronounced as to offer no difficulty whatever. This is true of the cases in which a history of one or repeated attacks of acute appendicitis is present, or in which pains of varying severity exist over the ileocecal region, either coming on periodically or of a persistent nature. This is, however, only true of the minority of cases. In the greater number of cases, the symptoms are very vague and, hence, offer great difficulty in diagnosis. In the majority of cases there is no definite history of an acute attack, either because such an attack existed during childhood, and, therefore, cannot be recalled by the patient, or because the acute inflammation gave rise to such insignificant symptoms as to be hardly noticeable. This is one important reason why there is so much difference of opinion as to whether vague gastric symptoms with spontaneous pain in the ileocecal region and tenderness should be attributed to chronic appendicitis or to some other cause. There are so many causes for pain in the ileocecal region with gastro-intestinal symptoms that the mere complaint of gastric distress and tenderness in the ileocecal region by no means justifies the rash conclusion that chronic appendicitis is the cause of it. Until ten or fifteen years ago surgeons and internists were ready to yield to the temptation, to consider it chronic appendicitis and advise operation, if the patient complained of pain in the ileocecal region and had gastric symptoms. The numerous disappointments, however, in which the removal of the appendix, even if the pathologist pronounced it diseased, brought no permanent relief, have rightly taught us to be more careful before we attribute the symptoms to chronic appendicitis.

The general recognition that a diseased appendix may produce definite symptoms of gastric and duodenal disorder with few or no localizing symptoms, is due to the study of the pathology in the living. Especial credit must be given to Moynihan,[9] the Mayos, Paterson and Fenwick. Moynihan has rightly termed these symptoms, "appendicular dyspepsia," a term accepted by men like Deaver, the Mayos, Lichty[10] and others.

Sir Humphrey Rolleston[11] divided correctly the symptoms into four groups: 1, Reflex; 2, mechanical; 3, toxic; 4, infective. This division corresponds so much to facts that it seems advisable to elaborate on it even more fully than is done in the original article by Rolleston. The question will at once suggest itself whether it is possible to judge the pathological changes in the appendix from

one of the four groups of symptoms. This is only possible to a very limited degree and mainly regarding the mechanical and infective groups of symptoms.

1. *Reflex.* According to Rolleston, to the reflex symptoms of chronic appendicitis belong those complaints which are characterized by hypertonus and spasm of the stomach, as well as failure to relax on the part of the pyloric or ileocecal sphincter, leading to gastric or ileal stasis, and so to excess of acid or to toxemia. That hypertonus and hyperperistalsis are often reflexly caused by the diseased appendix, and are responsible for the symptoms, is proved by the fact that Moynihan observed violent gastric contractions and spasm of the pylorus or other parts of the stomach in the presence of a chronically diseased appendix on the operating table, in cases of chronic appendicitis. Hurst[12] observed fluoroscopically spasm of the greater curvature if pressure is exercised over the ileocecal region. The same author also states that the delay in the ileum encountered in chronic appendicitis is due to spasm of the ileocecal sphincter.

The symptoms enumerated by Rolleston and the observations of Hurst indicate disturbed motor phenomena in the stomach and ileum, the result of chronic appendicitis. The disturbance in the motility of the colon, bringing about marked spasm of different parts of the colon, are also frequently associated with chronic appendicitis, thus explaining spastic constipation and sometimes the marked pain over the sigmoid. Chronic appendicitis does not always disturb the motor function in the gastro-intestinal tract and bring about hypertonus but it may also cause loss of tone in different parts of the gastro-intestinal tract. It is, therefore, no wonder that in a certain number of cases there is gastric atony which is responsible for most of the symptoms, or atony of the cecum (typhlatony) may be present. In these cases the atonic type of constipation is encountered, or, as is more rarely the case, constipation alternating with diarrhea. Very frequently there may be symptoms of hypertonus and spasm in some parts of the gastro-intestinal tract and loss of tone in other parts. It has been my experience that in chronic appendicitis there is often atony of the stomach and spasticity of the cecum or descending colon.

The sensory phenomena due to chronic appendicitis manifest themselves largely by the presence of pain in the epigastric region. The cause of reflex pain has given rise to some discussion. Sir James MacKenzie[13] maintains that it is referred to the peripheral termination of the sixth and seventh dorsal nerves in the abdominal wall, and that this depends upon the irritated focus in the spinal cord. Hurst argues that the pain is visceral in the pyloric end of the stomach and due to peristalsis. They agree, however, that the epigastric tenderness is due, not to pressure on the stomach, but to the irritated focus in the spinal cord which causes an exaggerated sensory

effect when the skin and especially the muscles of the underlying subperitoneal tissues are pressed upon. That the reflex pain is due to irritated focus of the spinal cord is evidenced by the fact that in certain cases of chronic appendicitis, the pain may be thoracic, even simulating stenocardia, if the irritating center is situated higher in the spinal cord, in the fourth or fifth dorsal nerves. The pain may also radiate down to the urinary bladder or even to the right thigh, simulating cystitis or sciatica, not due primarily to pressure on the nerves, as is often the case if the symptoms are of a mechanical nature, but due to the fact that the irritating center is lower in the spinal cord (last dorsal or lumbar nerves).

Reflex secretory phenomena resulting from chronic appendicitis are manifested in the majority of cases by disturbances in gastric secretions. In most cases there is hypersecretion and hyperacidity, which is chiefly of alimentary character. In a lesser number of cases there may be transient continuous hypersecretion. Lowered acidity in chronic appendicitis is much rarer. The reflex secretory disturbances may exert their influence upon the colon, giving rise to colica mucosa with the accompanying periodic attacks of cramps and the discharge of large quantities of mucous casts, or it may even spread to the salivary secretions causing increased salivation. In some cases it may influence the secretion of urine, giving rise to frequent urination. This, however, seems more likely to be the result of gastric hyperacidity with either diminished acid in the urine or even alkalinity of the urine which causes irritation of the urinary bladder and frequency in micturition, but no real increase in the quantity of urine. The transient increased hypersecretion in the colon may give rise to frequent attacks of serous diarrhea.

The reflex symptoms are not always alike in all cases of chronic appendicitis and they are not always alike even in the same individuals. In some the motor phenomena predominate, bringing about distress in the epigastrium and epigastric pressure soon after meals, persistent belching, regurgitation of sour fluid, peristaltic unrest in the upper quadrant of the abdomen and the different parts of the colon, especially in the cecum, rigidity of the cecum and even rigidity of the rectus overlying the cecum. Where there is a depression in the motor function of the gastro-intestinal tract, the symptoms of gastro-intestinal atony are encountered, consisting of sensation of persistent heaviness in the abdomen, the splashing sound over the stomach and cecum and other signs of atony in the cecum, such as gurgling which is persistent most of the time, and especially marked five or six hours after meals.

In other cases the sensory disturbances predominate. Such patients complain of pain out of proportion to all the other findings. The pain, as already stated above, may be epigastric or may even be thoracic, but what is very characteristic of the pain is the fact that, as was pointed out by Aaron, pressure over the appen-

dicular region brings about the pain in the area of which the patient spontaneously complains. Head's zone is also most marked over the appendicular region.

Where the secretory phenomena predominate there is marked pyrosis, regurgitation of acid secretion and sometimes even vomiting. The secretory type may sometimes simulate gastric or duodenal ulcer and makes the differential diagnosis clinically impossible. In reality it is not unlikely that the persistent hypersecretion leads to superficial gastric erosions and gastric symptoms, or even gastric or duodenal ulcer, which may heal upon the removal of the appendix. That this is so is verified by the studies of Roessle,[14] who brought pathological proof that ulcer of the stomach or duodenum is not infrequently the result of chronic appendicitis.

A number of other symptom-complexes have been attributed to chronic appendicitis which may also be considered of a reflex nature. The French School speaks of "appendicitis asthmatique," "appendicitis epileptique," "appendicitis cephalique," "appendicitis neurasthenique," and "appendicitis hysterique." Of course, such cases are rather rare, but they are undoubtedly encountered. That chronic appendicitis may sometimes be reflexly responsible for the most peculiar symptoms is illustrated by the following case:

Case I.—A woman, aged twenty-eight years, referred by Dr. J. J. Rosenberg, was subject to periodic attacks of oppression in the chest and hoarseness to the extent of almost complete aphonia. The physical examination of the chest was entirely negative. In view of the fact that the patient gave a history of having suffered occasionally from abdominal cramps, her family physician, insisted that a complete gastro-intestinal examination, including roentgenography, should be made. This examination disclosed evidence of marked adhesions in the ileocecal region with an abnormally situated elongated and persistently filled appendix, which was tender. Because of her protracted suffering, she herself insisted upon operation. Dr. A. A. Berg removed a severely diseased appendix. Several years have now elapsed since the operation and the patient has had no return of her symptoms.

The question now arises: Why does chronic appendicitis in a certain number of cases give rise to reflex symptoms and why do the reflex symptoms differ in different individuals and sometimes in the same individual? The answer to this question may lie in the fact that these individuals are primarily afflicted with disturbances in the vegetative nervous system. In most of these sufferers all or some of the following symptoms may be encountered: the patient is usually of tall, frail stature, with long neck, long, flat thorax, floating tenth rib, poorly developed musculature and enteroptosis with infantilism of the genital organs. The objective signs are: glistening, prominent eyes, wide lids, hypertrophied follicles at the

base of the tongue, moist cold hands and also cold feet; dermagraphy is present, the pulse is as a rule slow, salivation is increased and there may be lachrymation. In other words, they are afflicted with some or all of the symptoms which, according to Eppinger and Hess,[15] are the expression of vagotonia. Pure vagotonia is, however, very rare. In most individuals with disturbance of the vegetative nervous system there are both vagotonic and sympathicotonic symptoms. In a patient afflicted with disturbances in the autonomic nervous system suffering from appendicitis, no matter what the pathological changes in the appendix may be, the reflex disturbances caused by the hypersensitiveness of such an individual are much more pronounced than the local symptoms. This is the reason why it is so difficult to differentiate purely functional symptoms with stigmata in the vegetative nervous system from those of an organic disease aggravated and masked by the symptoms caused by the unbalanced autonomic nervous system.

In these hypersensitive individuals, the local disturbance of the appendix may be very insignificant and still cause very unusual symptoms. On opening the abdomen, a small obliterated appendix or, on incising the appendix small erosions of the mucous membrane may be found, or the appendix may be found to be filled only with fecal stones and mucus and one may wonder why such insignificant pathological changes in the appendix should have caused such an array of symptoms.

This group of cases offers great difficulty in the differential diagnosis. If the diagnosis is made, the frequent question arises, whether the removal of the appendix will actually remove the symptoms. In reality, the removal of the appendix may only do away with the symptoms for a short time and this is the reason why controversy has resulted as to whether appendicitis with mild local symptoms and marked reflex disturbances should be considered a surgical disease. If, however, the fact that any local affection often aggravates the symptoms caused by an unbalanced nervous system is taken into consideration, it becomes evident that it is not at all unwise to remove the disturbing cause. Permanent favorable results can only be obtained if proper attention is also paid to the congenitally inferior autonomic nervous system.

2. *Mechanical.* The mechanical symptom-complex may be caused by two factors: (*a*) by the presence of foreign bodies in the lumen of the appendix proper, and (*b*) by appendicular adhesions to the neighboring organs.

(*a*) To the former belong the cases in which fecaliths or parasites are lodged in the appendix. There has been considerable discussion as to whether the substances named above can be responsible for chronic appendicitis. In agreement with Aschoff, it may be stated that primarily they would not cause symptoms, but in the presence of ulceration in the appendix or other chronic inflam-

matory changes within the lumen of the appendix, these foreign bodies may give rise to repeated attacks of appendicular colic or even persistent discomfort in the ileocecal region. Foreign bodies, such as stones, worms or seed lying in a healthy appendix may cause no symptoms at all or at most only mild attacks of transient pain in the ileocecal region.

It has already been mentioned above that intestinal worms are considered by some to be a very important factor in the causation of acute and chronic appendicitis. Their importance as a primary cause is very doubtful but if worms are present in a diseased appendix, they may give rise not only to the symptoms of chronic appendicitis but also to the annoying symptoms characteristic of intestinal parasites such as nausea and excessive appetite. The patient has a sallow face, and there is an increase of eosinophiles in the blood. Worms in the appendix may sometimes explain why, even after complete elimination of the worms from the intestines, the symptoms still persist. A case of this character observed by me was operated upon by Benjamin T. Tilton in Har Moriah Hospital.

(*b*) The second group causing mechanical symptoms is the one due to adhesions, and this is by far the most important. The symptoms in these cases depend considerably upon the extent of the adhesions. In most cases, adhesions usually spread to the cecum, causing perityphlitis. Such patients usually complain of fulness in the cecal region and pain of varying severity. The abdominal wall over the region of the cecum is usually tender and quite often the Bastedo sign (inflation of the rectum, causing pain over McBurney's point), or the sign pointed out by Reder (digital examination of the rectum causing pain over the McBurney's point), is present in these cases. Adhesions between the ileum and cecum often cause pain in the left hypochondrium, the result of ileocecal valve incompetency (Cole). Sometimes adhesions extend into the right hypochondrium, causing traction and kinking of the hepatic flexure, or they may often spread to the liver and gall-bladder, simulating biliary disease and giving rise to moderate subicteric discoloration of the sclera, increased bilirubin in the blood serum, and, transiently, even show the presence of a small quantity of bile in the urine. The adhesions may also spread to the lumbar region, causing pressure on the ureter, simulating renal or ureteral colic, and may even cause the appearance of red blood cells in the urine or sometimes even hematuria. Cases are mentioned in literature where the adhesions have caused pressure on the sciatic nerve, resulting in persistent sciatica which disappeared entirely after the removal of the diseased appendix.

Chartier[16] mentions a case of an enlarged chronically inflamed appendix, the lumen of which contained pus, and which caused pain and hyperesthesia and weakness in the left limb, circumscribed

pressure pain over the fourth lumbar vertebra and severe paroxysmal pain over the lumbar region.

The adhesions may spread to the female generative organs, leading even to sterility.

The adhesions may sometimes give rise to the formation of dense bands, causing kinking of the cecum and pulling of the cecum downward to the symphysis, or, what is more common, a pulling of the cecum upward and backward. The bands may sometimes spread from the ileum to the cecum, causing a distinct Lane's kink, or they may encircle the cecum, giving rise to intermittent progressive intestinal obstruction. In these cases, the symptoms are those of chronic intestinal obstruction. Constipation becomes obstinate; even laxatives and enemas have but little effect. Sometimes transient diarrhea may be present, which may be due to the catarrh of the colon caused by the scybalous feces or the diarrhea may be the result of the fluid stool passing through, whereas the solid feces stagnate. Such patients have a moderately distended abdomen, are often nauseated, and have frequent attacks of colicky pains due to peristaltic unrest. In severe degrees of obstruction there may be continuous rumbling in the colon. Dense adhesions in the ileocecal region may cause the patient pain if he lies on the left side. In some cases the adhesions cause contraction of the cecum, and if the cecum becomes distended with gas there is invariably pain. Such patients are usually very uncomfortable when constipated. In other cases the adhesions cause distention in the cecum, and these patients are more comfortable when constipated, because after evacuation of the bowel the cecum collapses, causing traction on the peritoneal bands.

At times the adhesions around the appendix may give rise to a distinct palpable mass, simulating a tumor in the ileocecal region. In these cases, the differential diagnosis between ileocecal tuberculosis, primary tuberculosis of the appendix, and primary carcinoma of the appendix, as well as actinomycosis of the appendix, comes into consideration. Primary tuberculosis and primary carcinoma of the appendix are diagnosed only upon the operating table. There is hardly a case on record where the diagnosis was made before operation. The diagnosis of ileocecal tuberculosis will be discussed in connection with the roentgen-ray diagnosis of chronic appendicitis. Actinomycosis of the appendix is rare. It is characterized by its chronicity, by the fact that the skin overlying the appendicular region becomes adherent to the abdominal wall, and by the presence of actinomycosis elsewhere in the body. The objective diagnostic signs of chronic appendicitis resulting from adhesions are best disclosed by the roentgenography, which will be discussed later.

3. *Toxic.* Rolleston states that the absorption of bacterial toxins from the appendix may set up general toxemia and even cause

myocarditis, and damage to the mucous membrane in the stomach and intestines, and thus give rise to hemorrhage. To what extent toxic absorption from the diseased appendix may give rise to general toxemia it is very hard to tell. The fact, however, that chronic appendicitis sometimes gives rise to severe gastric hemorrhage (parenchymatous hemorrhage—Dieulafoy) must be strongly emphasized. Fenwick[17] assumes the hemorrhage to be of toxic nature. Soltan believes that the hemorrhage is due to the fact that the gastric mucosa is penetrated by protracted hypersecretion and hyperacidity to the point of erosions of the stomach. This is, however, very doubtful. Whether the hemorrhage is of toxic nature or not cannot be stated with certainty. The 3 cases of gastric hemorrhage the result of chronic appendicitis observed by the author, all of which were operated upon, seem to indicate that the bleeding is, in reality, more of hemolytic origin (caused by toxins) than of any other known source. The hemorrhage is profuse, its control difficult, it has no tendency to respond to treatment, and there is a rapidly developing anemia.

To the toxic symptoms may also be added those symptoms of chronic appendicitis which simulate endocrine disturbances, especially hyperthyroidism. Much more rarely may chronic appendicitis simulate Addison's disease. A case of this nature was seen by the author and deserves brief mention.

Case II.—A woman, aged thirty-four years, a mother of three healthy children, gave a history of two definite attacks of acute appendicitis six years before. She came with symptoms of severe asthenia, marked loss of weight, dark skin, and also discoloration of the mucous membrane of the mouth. The blood-pressure was very low, and vomiting was very marked. She had an increased tolerance to sugar. The case, therefore, had all the earmarks of Addison's disease. In view of the fact, however, that she also had severe tenderness in the ileocecal region with marked resistance and a suspicion of a palpable mass, the gastro-intestinal tract was roentgenographed. It showed marked ileocecal stasis and incompentency of the ileocecal valve. Because of the extreme asthenia and secondary anemia, the patient was transfused twice and after slight improvement an operation was advised. She was operated on by Dr. A. A. Berg. Extensive adhesions in the ileocecal region and a very thick and enlarged appendix were found, the lumen of which was filled with pus. Convalescence was rather stormy. The patient was in collapse after the operation for several days, but active stimulation, continued Murphy's drip, and a third transfusion made the patient rally and eventually she recovered completely.

4. *Infective.* That microörganisms, especially streptococci, lodging in a diseased appendix, may give rise to symptoms of mild infection is not surprising. The microörganisms may spread to the

neighboring organs, and cause chronic pyelitis or they may spread to the gall-bladder causing chronic cholecystitis. Rolleston states that chronic bacterial infection of the appendix may give rise to small pulmonary emboli and pleurisy and local thrombophlebitis of the iliac veins. The symptoms of the infective group are: tiredness, moderate elevation of temperature especially after exercise, chilliness, and increased pulse frequency. The symptoms may even simulate pulmonary tuberculosis. Schnitzler[18] states that pulmonary tuberculosis often leads to symptoms simulating chronic appendicitis without any local changes in the appendix. In expressing this opinion he takes the stand exactly opposite to that of some of the French surgeons, who state that chronic appendicitis may often give rise to symptoms simulating pulmonary tuberculosis, and the removal of the appendix causes a disappearance of the symptoms. The view of the French School would appear to be the sounder one.

Diagnosis. In the diagnosis of chronic appendicitis, the history of one or more acute attacks plays a very important rôle. In the absence of such a history, the diagnosis become difficult. From the symptoms alone it is hard to make a diagnosis. As to the objective findings, the following are of importance:

(*a*) Tenderness in the ileocecal region.

(*b*) Rigidity over the right rectus muscle is present even in some chronic cases, as rightly pointed out by Ransohoff.[19] This is especially marked if there are adhesions around the cecum.

(*c*) The diagnostic value of gastric secretions in chronic appendicitis is estimated differently by different authors. Fenwick states that if there is ulceration in the mucous membrane of the appendix there is usually hyperacidity. If chronic appendicitis is complicated by adhesions there is usually subacidity. According to our experience, chronic appendicitis is much more often associated with hyperacidity than with subacidity, irrespective whether it is complicated by adhesions or not.

(*d*) Aaron's sign: pressure in the appendicular region causing pain in the epigastrium.

(*e*) Bastedo sign: tenderness over the ileocecal region on inflation of the colon. This is present in a limited number of cases, and chiefly in those in which chronic appendicitis is complicated by adhesions.

(*f*) Tenderness over the appendicular region on the administration of an enema, likewise rare.

(*g*) The Reder sign: tenderness over the appendicular region upon rectal examination, also very rare.

(*h*) Rovsing's sign: pain over the appendicular region if pressure is exercised over the left side at a point corresponding to the McBurney's point on the right side.

It was observed by the author that in case of retrocecal appendi-

citis the pain, although persistent over the right loin if pressure is exerted there, is referred to the appendicular region.

Roentgenography. Much importance must be attached to the roentgenography in the diagnosis of chronic appendicitis, and, hence, a few remarks about the roentgenological appearance of the normal cecum and appendix may be in order, to have a proper understanding of the pathology.

Normally, the contrast meal reaches the cecum two to four hours after the ingestion of the meal, and the last remains of the meal leave the small intestines after eight to nine hours. The normal cecum, as well as the ascending colon, do not show deep segmentations. The segmentations are only about half as deep as the haustra of the transverse colon. The cecum is about 7 cm. long and is separated from the ascending colon by the tenia mesocolica. This boundary, however, cannot be seen, as a rule, on the skiagraph unless the habenula caeci which form these tenia are especially marked. Normally, about half of the cecum is situated in the right iliac fossa. If the cecum moves almost to the median line when the patient is turned on his left side, one may speak of cecum mobile. This is mentioned because, according to Wilms, it plays an important rôle in the differential diagnosis, as it gives rise to symptoms simulating chronic appendictis.

The lowest point of the cecum when the patient is in an upright position lies about one or two finger breadths above the center of the acetabulum. Because the mesentery of the cecum is longer, it is more or less freely movable upward and downward.

Until 1911, it was assumed that the appendix could not be visualized roentgenologically. It is probably due to the fact that the earlier work was done by means of the Rieder contrast meal. When the thin meal, especially buttermilk suspension, was introduced, the visualization of the appendix became common. The first to have described the appendix roentgenologically were Quimby,[20] Case,[21] Imboden,[22] Eisen,[23] Cohn,[24] Hurst,[25] Groedel,[26] as well as Schwartz, Stierlin, and others.

There has been a great deal of discussion as to whether the filling or the nonfilling of the appendix with the contrast indicates disease. There is almost universal agreement today that no conclusion as to its pathology can be drawn from the filling or nonfilling of the appendix. Some assert that early in life, up to the age of about twenty years or even thirty, if the appendix does not fill it indicates disease, whereas beyond forty the normal appendix should be obliterated, and, therefore, if it fills, it indicates disease, but since such assertions do not correspond to facts, they have no clinical or diagnostic value.

The position and the length of the normal appendix varies considerably in different cases and at different times, which definitely shows that the appendix has independent motility and mobility. This is important because if the appendix manifests the same shape and position

persistently it is an indication that it is fixed by adhesions. Besides the motility of the appendix in toto at its mesenteriolum, definite peristaltic contractions in the wall of the appendix may be seen, which often make the appendix appear separated into different portions. Cohn, and, later, Grigorieff, were the first to point out the fact that the appendix may fill and empty repeatedly if the patient is studied periodically while the contrast meal traverses the entire gastro-intestinal tract. This can absolutely be confirmed.

Because of the importance of the competency of the ileocecal valve in the diagnosis of chronic appendicitis and other lesions in the ileocecal region, a few remarks must be made on this subject. Case,[27] Dietlin and Groedel were the first to attribute clinical importance to ileocecal valve incompetency. Case began his observations in 1910. He found the valve to be incompetent in about one-sixth of all cases examined with the enema. For the most part the patients examined were suffering from gastro-intestinal symptoms and those of complications of constipation. Dietlin believes that the valve is usually competent in children and adults, and incompetent in infants. Incompetency is generally an indication of disease in the iliac region. The work of Keith, and later of Rutherford, proves that the ileocecal valve is normally competent. Carman states that the enema enters the ileum in the greater majority of cases, probably about nine-tenths. The patients examined are of the character usually sent for roentgenography test; they complain of gastro-intestinal symptoms of some sort. But there are also a considerable number whose symptoms are found on operation to be due to other abdominal disease, not affecting the bowel, which is found normal. Carman found of all degrees incompetency ranging from trivial backflow from the valve to an extensive filling of the lower ileum, without any relation between this insufficiency and the pathological condition of the ileocecal region being noticeable.

For the roentgenological study of the diseased appendix, both the direct and the indirect signs must be utilized. The value of the direct signs was most carefully studied by Spriggs and Marxer[28] and, according to them, in order to determine directly whether the appendix is diseased or not, one must pay attention to the filling and emptying of the appendix, its shape, mobility, position, hyperactivity, spasm, tenderness, and the presence of concretions. In order not to miss the direct visualization of the appendix, the patient must be examined fluoroscopically and the appendix should be palpated under the fluoroscope after six, eight, twenty-four, forty-eight and seventy-two hours, and sometimes even beyond that time after the cecum is entirely empty, in order not to overlook a retrocecally situated appendix. The normal appendix may empty and fill repeatedly during the course of the examination by means of the contrast meal. If the appendix remains persistently filled after the entire gastro-intestinal tract is empty, there is reason to attribute to it a pathological significance.

As to the shape, the abnormal appendix may sometimes be short and thick, sometimes almost as wide as it is long, the shape and position not altering throughout the entire course of the examination. The shortness and thickness do not necessarily indicate that the diseased appendix is not longer than what is seen on the roentgenogram, but it does indicate that the lumen of the appendix is obliterated in its center, and, therefore, only the upper part fills with contrast substance. The appendix may be unusually long, thick and persistently filled.

The position of the appendix varies even physiologically, and a malposition of the appendix is of pathological importance only if the appendix is at the same time fixed and tender. Certain malpositions of the appendix, however, invariably indicate pathology, and these are: if the appendix is pulled to the left side, or pulled low down into the pelvis, or to the region of the urinary bladder, or up to the retrocecal region.

Tenderness over the appendicular region, fluoroscopically observed and when persistently present, is of great diagnostic significance. The presence of concretions indicates disease only if other symptoms and signs of chronic appendicitis are present. If the appendix is persistently kinked and does not alter its position, it is likewise an indication of disease.

The other direct signs are the result of the adhesions caused by the diseased appendix. These are: either a very low or very high position of the cecum, restricted mobility of the cecum, pulling of the sigmoid to the right or pulling of the cecum to the left, sometimes traction and pulling of the transverse colon downward, and kinking of the hepatic flexure.

If the adhesions are such as to cause matting of the ileum with the cecum, there is marked delay in the emptying of the ileum, even beyond twenty-four hours. The traction of the adhesions on the ileocecal valve causes it to become patulous, resulting in ileocecal valve incompetency. Very frequently there is gas in the lower ileum on account of ileocecal adhesions.

The indirect roentgen-ray signs of chronic appendicitis in the sequence of frequency are: ileal stasis not due to adhesions, but the result of spasm of the ileocecal valve (Hurst); ileocecal valve incompetency, due to failure of the ileocecal valve to close; stasis in the cecum after the entire colon is empty; spasticity or atony of the cecum, spasm in the pylorus, and, finally, spasm of the greater curvature of the stomach if pressure is exercised on the appendicular region (Hurst). The last is a very rare finding, according to my experience, but it may be present in vagatoniacs afflicted with chronic appendicitis. At times enterospasm or spasm of the descending colon is associated with chronic appendicitis.

Very rare indirect roentgenological signs are marked paralysis of the cecum (typhlatony) or a very movable cecum.

The gastric motility in chronic appendicitis varies a great deal, depending entirely upon the tone of the stomach. Spasm of the pylorus or of the sphincter pylori in chronic appendicitis causes, as a rule, no delay in the emptying of the stomach. If there is considerable gastric atony in connection with chronic appendicitis, there may be marked delay in the emptying of the stomach.

Differential Diagnosis. From the diagnostic, as well as from the therapeutic, standpoint, it seems most practical to discuss the differential diagnosis under the following divisions: (1) Diseases which simulate chronic appendicitis, the appendix being normal; (2) diseases resulting from chronic appendicitis; (3) where the primary disease had its starting point in another intra-abdominal viscus, eventually affecting also the appendix.

To the first group belong the following diseases: Hysteria, as well as neurasthenia, which may cause persistent pain in the ileocecal region with gastro-intestinal symptoms of varying intensity. Such cases are very trying, and only too often they are submitted to surgical intervention, the operation disclosing a normal appendix. Hysterical individuals may even lose all their symptoms after the removal of the appendix, these being purely the result of psychologic influence. Neurasthenic individuals, on the other hand, with general atony of the gastro-intestinal tract and typhlatony in particular, remain with the same symptoms after the removal of the appendix.

The differential diagnosis between hysteria and neuresthenia with appendicular symptoms (pseudo-appendicitis) and that of true chronic appendicitis is often impossible. Therefore, in all neuropathic individuals hysterical stigmata should be carefully looked for. In neuresthenics marked atony of the cecum does not cause any rigidity in the ileocecal region, but makes the cecum feel rather doughy upon palpation and there is, in most cases, gurgling in the cecum. The roentgen-ray examination shows an unusually dilated cecum filled with gas and sometimes even fluid.

Another functional disease which frequently simulates chronic appendicitis is enterospasm, either of the entire colon, or only parts of the colon. This has been particularly pointed out by Lieck.[29] If the spasm involves the entire colon, whether due to lead poisoning, tabes dorsalis, intestinal parasites, chronic colitis, or enteritis membranacea, or whether of functional origin, as in colica mucosa or pure vagotonia, there is usually no difficulty in the differential diagnosis. If, on the other hand, the spasm is confined to the cecum, whether due to typhlitis or of a functional nature, the diagnosis is very difficult and quite often impossible.

Some differentiating points may assist in arriving at a proper diagnosis. Spasm of the cecum, the result of typhlitis, often causes most discomfort if the patient partakes of an excess of vegetables. The pain is usually most marked four to six hours after a meal,

at the time when the food reaches the cecum. Spasm of the cecum of a functional nature causes persistent pain, and, on careful palpation, one may succeed in outlining the rigid cecum. Roentgenological examination is of great value in these cases, showing as it does, the haustra of the cecum very plainly. Normally, the cecum does not show these haustrations. Here, the cecum, instead of being about twice the width of the descending colon, as in normal cases, is as narrow as the descending colon, or even narrower. The spasm of the cecum interferes with the contrast enema completely filling out the cecum, and sometimes it may not fill in at all. In other words, delay in retroperistalsis is very prolonged. The contrast taken by the mouth shows small spots of barium in the contracted cecum sometimes for days after the entire colon is empty.

The movable cecum (cecum mobile—Wilms) may simulate chronic appendicitis. This, however, is generally associated with general loss of tone and unusual mobility of the other abdominal organs. If the patient is examined fluoroscopically while lying on the left side, the cecum is seen to move two or three fingers' breadth to the left of the median line. Of course, spasm and atony of the cecum, as well as cecum mobile, may be secondary to chronic appendicitis.

Another disease which may be classified as functional and sometimes simulates chronic appendicitis is the movable or floating right kidney. This may give rise to appendicular pain, but a careful examiner will hardly have any difficulty in making the differential diagnosis.

Of the organic diseases of the cecum, giving rise to difficulty in the diagnosis, the following are to be considered: tuberculosis, carcinoma and actinomycosis of the cecum and ileocecal tuberculosis. Tuberculosis of the cecum and ileocecal tuberculosis are usually associated with tuberculosis elsewhere in the body, and the roentgenological examination, as first brought out by the studies of Stierlin[30] and, later, by Brown and Sampson,[31] offers considerable aid in differential diagnosis.

The cecum and ascending colon fail to hold the contrast substance or only do so partially, and, hence, the cecum may not be visualized at all or only in the form of a narrow, partially filled spastic tube throughout the entire course of the gastro-intestinal roentgenological examination (Stierlin). There is, in addition to that, hypermotility of the small intestines and colon (Brown,) and frequently iliac stasis. Pirie, and recently Levy and Haft, have confirmed Stierlin's observations, as have most authors.

Carcinoma of the cecum as a rule offers no difficulty in diagnosis, as it usually presents on palpation a hard and palpable mass in the cecal region. Actinomycosis of the cecum can only be diagnosed if the process spreads to the skin, causing the skin to become adherent to the underlying structures, and if actinomycosis can be found in other parts of the body.

A very rare disease of the cecum simulating appendicitis was

recently reported by Cooke.[32] The operation disclosed the cecum to be the seat of multiple diverticuli which harbored a concretion. As this concretion increased in size it caused pressure, necrosis and an extensive inflammatory deposit.

Another rare affection simulating chronic appendicitis is tuberculous glands in the ileocecal region, without affection of the cecum or ileum, especially if these glands cause pressure on the ileofemoral nerve. This is much more common in younger individuals than in those of adult life. I have encountered cases where scoliosis of the lumbar region, either congenital or acquired, may give rise to pains in the appendicular region. The acquired form of scoliosis of the lumbar region may be encountered in hip disease or in atrophy of the muscles of the hip and thigh, the results of poliomyelitis. Of course, in these cases, the history, the general physical examination and the roentgenological examination of the lumbar vertebra, will guard against mistake.

Finally, diseases of the right ovary and tube, as well as diseases of the prostate, may simulate chronic appendicitis. Chronic appendicitis may also be simulated by stones in the right kidney and especially in the right ureter. This is especially true in cases where the stone lodges in the kidney or ureter, not passing into the bladder. Here, too, a careful examination of the urine, the positive Murphy sign, tenderness over the right testicle, and above all, the roentgen-ray examination, and, if necessary ureteroscopic examination, will aid in establishing the proper diagnosis.

To the second group, diseases resulting from chronic appendicitis, belong functional gastro-intestinal diseases secondary to chronic appendicitis, organic intra-abdominal diseases secondary to chronic appendicitis, extra-abdominal diseases, and other diseases of the appendix.

The functional diseases are hysteria and neurasthenia. It cannot be too strongly emphasized that just as hysteria and neurasthenia may simulate chronic appendicitis, so may chronic appendicitis, by causing persistent suffering, lead to hysteria and neurasthenia in a predisposed individual.

Spasm of the cecum may also be secondary to chronic appendicitis in predisposed individuals. The relation of calcium metabolism to persistent spasmophelia in the adult was clinically pointed out by Perez[33] in Berlin, and was later experimentally demonstrated by Krauss and Zondek. Recently, Kauffmann[34] contributed a very interesting article on this subject. If spasmophilic individuals develop any organic disease, the spastic phenomena are so pronounced that the underlying organic disease may be overlooked, or, if such individuals develop a marked organic disease the spastic phenomena may be aggravated and the differential diagnosis is, therefore, sometimes quite impossible.

To the functional gastro-intestinal diseases secondary to appendicitis belong the functional secretory, sensory and motor disturbances

of the stomach and colon. The functional secretory, sensory and motor disturbances in the stomach secondary to chronic appendicitis may be such as to fully simulate gastric or duodenal ulcer. In severe cases they may even cause marked delay in the emptying of the stomach. The differential diagnosis is made possible in most cases by the roentgen-ray examination, which aids in excluding gastric or duodenal ulcer, and shows some or all of the roentgenological signs characteristic of chronic appendicitis named above.

Chronic appendicitis may sometimes cause secretory and motor disturbance in the colon, giving rise to colica mucosa, marked enterospasm, or even severe constipation, or sometimes constipation alternating with diarrhea, and in rare cases, only diarrhea.

The intra-abdominal diseases secondary to chronic appendicitis deserve special mention, as both pathology and clinical studies have taught us that chronic appendicitis may be the cause of ulcer of the stomach (Roessle) or of gall-bladder infection (Moynihan, Mayos, Rolleston), and cause widespread adhesions, giving rise to varying degrees of colonic and iliac stasis. These diseases need no further discussion here as they have been sufficiently discussed above. Of the intra-abdominal diseases giving rise to secondary chronic appendicitis, affections of the female generative organs, especially that of the right tube and ovary are of practical consideration. The differential diagnosis, as a rule, is not difficult, if careful vaginal and rectal examinations are systematically carried out.

It must be emphasized again that the statement of Sahli, that the appendix is the abdominal tonsil, which, if diseased, is productive of a great deal of evil, undoubtedly holds good. This evil effect not only makes itself felt in the intra-abdominal viscera, but may also cause extra-abdominal disease.

Among the extra-abdominal affections may be mentioned chronic joint diseases, some endocrine diseases (thyrotoxicosis and, very rarely, Addison's disease). It may also be mentioned that chronic appendicitis is at times associated with right-sided pleurisy. How this occurs was explained by the experimental studies of Putzianus,[35] who demonstrated that an infection of the lymph vessels of the cecum and appendix sometimes results in right-sided pleurisy, whereas infection of the cecal veins never cause pleurisy. This may explain the case quoted above where there were attacks of hoarseness, possibly due to mediastinal pressure on account of lymphatic infection of the mediastinal pleura, the result of chronic appendicitis, and in which the symptoms disappeared after the removal of the appendix.

Some authors have also encountered frontal sinusitis and pansinusitis, the result of a chronically infected appendix.

Other diseases of the appendix which simulate chronic appendicitis are: primary tuberculosis, primary carcinoma and primary actinomycosis of the appendix. These diseases are, in most cases, not diagnosed before operation.

Prognosis. From what has been said above, the prognosis depends on a great many factors. That chronic appendicitis may give rise to an acute exacerbation with all its dangers, is well known. Chronic appendicitis uncomplicated by functional disturbance or by adhesions or by other organic disease of the gastro-intestinal tract gives a good prognosis, if the appendix is removed. If, on the other hand, it is harbored by a neuropathic individual, the outlook depends entirely as to what is primary and what is secondary. If chronic appendicitis is primary, the removal of the appendix will likewise remove the symptoms. If, on the other hand, the neuropathy is primary, the removal of the appendix is of but little benefit. The primary disease must be treated in order to obtain results. If chronic appendicitis is the cause of adhesions, the prognosis depends considerably upon the position of the adhesions, and whether they can be surgically treated or not, and likewise upon the judgment of the surgeon handling the adhesions.

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DISEASE OF THE MEDIASTINUM AND ITS CONTENTS.

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Until comparatively recent years there was no region within the body in a more nebulous state, insofar as our diagnostic capabilities were concerned, than that relatively small region within the thorax, the mediastinum. Within this small area are contained many varied structures, each capable of undergoing pathological changes in the early stages with no symptoms whatever being manifested, and only showing evidence of these changes when they are very extensive, shortly before death. Or should symptoms be present early, they are as likely to be produced by pressure on some other structure within the mediastinum as they are by the offending structure itself. Because of its former inaccessibility to diagnostic procedure, it has been held sufficient to designate any condition with a symptom-complex referable to the mediastinum, as mediastinal tumor, without attempting to make a true pathological and anatomical diagnosis. The many advances made in our diagnostic armamentarium in recent years, have made it possible at the present day to diagnose rather concisely the nature of lesions within the mediastinum as well as its anatomical location.

The mediastinum is that space lying between the right and left pleura laterally, and extending from the sternum anteriorly to the vertebral column posteriorly. A line running from the junction of the manubrium and body of the sternum anteriorly to the lower part of the body of the fourth thoracic vertebra posteriorly, divides this area into a superior mediastinum, that space above the line bounded by the manubrium in front and the upper four thoracic vertebræ posteriorly, and a space below the line. This lower area is divided by the pericardium into an anterior mediastinum lying in front of the pericardium, a middle mediastinum containing the pericardium and its contents, and a posterior mediastinum lying behind the pericardium. The middle mediastinum containing the heart is by far the largest of these subdivisions.

The anterior mediastinum is very small because of the reflections of the pleura anteriorly, which go behind the manubrium from the sternoclavicular joints on either side to the middle of the sternum at the junction of the manubrium and body of the sternum; from there to the fourth costal cartilage, both pleural membranes being in contact, and at this point the right layer continuing down to the xiphoid process, while the left layer diverges slightly laterally and continues down to the sixth costal cartilage. Within the mediastinum are contained normally the thymus, trachea, bronchi, esophagus, heart and great vessels, lymph nodes, thoracic duct and

the vagus, phrenic and sympathetic nerves. At times it may also contain an enlarged thyroid or an accessory thyroid.

In order to diagnose conditions arising within the mediastinum, a knowledge of the pathological conditions that can occur within this space must be known. These may be under three headings:

1. Inflammatory.
2. Traumatic.
3. New growths.

Inflammatory processes within the mediastinum and its contents may be either acute or chronic. It is impossible to detect simple acute mediastinitis unless the acute condition is suppurative. This condition is not uncommon, and practically always is secondary to some other disturbance within the body. It may occur through extension from pneumonia or some other inflammatory condition of the lung or pleura, from osteomyelitis of the bony thorax or cervical or thoracic vertebræ, from an inflammatory condition in the deeper structures of the neck, especially a retropharyngeal abscess, from suppuration of the mediastinal lymph nodes or from an ulcerative process within the trachea, bronchi or esophagus. It may occur as a metastatic lesion in the course of a septicemia or erysipelas. It may follow trauma to the thorax with or without perforation of its wall and lodgment of foreign bodies within. Occasionally a case is met with in which no etiological factor can be discovered, and should be considered as a case of primary suppurative mediastinitis.

Generally the pus in this condition is localized or encysted in the anterior, middle or posterior mediastinum or laterally in the mediastinum. Rarely the entire mediastinum is involved in the process. When the pus lies in the anterior mediastinum it is very difficult of detection, as it lies directly beneath the sternum and in front of the cardiac outline, and gives little in the way of signs or roentgen-ray evidence. When involving the middle mediastinum there is, of course, a purulent pericarditis greatly widening the cardiac outline. The pus in the pericardial sac may be either encysted in one part of the sac or generalized. In the posterior mediastinum the condition generally is due to disease of the spine or lodgment of foreign bodies. Laterally in the mediastinum, it is usually subsequent to pneumonia. These abscesses within the mediastinum may rupture into any of the structures contained there, causing fatal hemorrhage or other septic conditions, or they may penetrate through the chest wall.

Chronic mediastinitis is simply a low-grade inflammatory condition without production of pus. It is evidenced by marked distortion and twisting of the structures within the mediastinum, due to extensive fibrous tissue replacement of the tissue normally present. It may result from the acute suppurative condition, but generally results from extension of a pleuropericarditis, tuberculosis,

syphilis or rheumatic conditions. Occasionally it is due to actinomycosis.

Traumatic lesions of the mediastinum occur not infrequently. Foreign bodies, such as bullets, may penetrate the thorax and lodge within the mediastinum, sharp instruments may pierce the chest and enter the mediastinum, or fragments of broken bones may lacerate the mediastinal tissues. Such injuries as these result in abscess formation in a large percentage of the cases, or abscess may result from an injury to the thorax without perforation into the mediastinum. Foreign bodies may lodge within the trachea or its bifurcation, or the esophagus, and cause secondary inflammatory conditions. As a result of trauma there may be found a good sized hematoma within the mediastinum.

A somewhat more serious result of trauma is the occurrence of mediastinal emphysema. This condition arises most commonly secondary to pulmonary disease or whooping-cough. It also occurs following operations at the base of the neck, especially for tuberculous glands or thyroid disease, or following tracheotomy. It may occur, following ulceration of the trachea or esophagus, by processes within these structures.

An unusual cause is artificial pneumothorax. The air may localize within one of the mediastinal spaces, such as within the pericardium or within the anterior mediastinal tissue. It may, however, be more extensive and spread into the superficial tissue of the thorax and into the neck.

The greatest number of pathological processes occurring within the mediastinum, come under the heading of new growths, benign or malignant. Benign growths are quite infrequent in occurrence, and include fibroma, myoma, lipoma, myxoma, chondroma, osteochondroma, simple cysts, dermoids, hydatids, teratoma, neuroma, hematoma and gumma. Of the benign tumors, the dermoid cyst is probably the one most commonly found. As a rule, it occurs in young adults, generally being located about the hilus area or just below, and being either single or multiple. Should it contain teeth or bone tissue, it renders the diagnosis a simple matter. Hydatids when found are generally in association with hydatid disease elsewhere within the body. Lipoma is probably the next most frequent of the simple growths, and these may obtain tremendous proportions. Fibroma may arise from the sternum or cellular tissue of the mediastinum. Chondroma and osteochondroma are rare, and arise from the sternum, costal cartilages or vertebral column. Hematoma may be found of large size. It may result either from trauma or one of the blood diseases, such as purpura. Sometimes it occurs in the course of one of the acute exanthemata. The remaining benign growths, including the gumma, are very rare and not capable of diagnosis, other than as a mediastinal tumor, except at operation or postmortem.

Malignant growths of the mediastinum are of much greater frequency than benign growths. Males predominate over females as to the occurrence of these tumors in the ratio roughly of $2\frac{1}{2}$ to 1. The sarcoma occurs more frequently than does the carcinoma. Sarcoma arise from the connective tissue of the mediastinum, lymph nodes or thymus. Carcinoma arise from the epithelium of the esophagus, trachea, bronchi, thymus or accessory thyroid.

It will probably be easier to consider these malignant growths according to the structure within the mediastinum from which they arise, together with other conditions that may occur within these same structures. Thus, in the glands, in the following conditions enlargements occur:

1. Simple lymphoma, inflammatory, as after measles; typhoid or whooping-cough, tuberculosis, syphilis or in pneumoconiosis.
2. Leukemia, lymphatic, myelogenous or pseudo.
3. Lymphadenoma.
4. Hodgkin's disease.
5. Lymphosarcoma.
6. Metastatic involvement.

The thymus may enlarge, due to simple hypertrophy, cysts, lymphosarcoma or carcinoma. The trachea and bronchi may have papilloma, chondroma or carcinoma. The esophagus may show diverticula, cardiospasm, stricture, either malignant, traumatic or specific, or congenital atresia. It may also show a tracheo-esophageal fistula.

Arising from the nerves we may find neuroma, ganglioneuroma, glioma or neuro-epithelioma. Occasionally there occurs a tumor within the mediastinum, due to enlargement of the thyroid either from simple hypertrophy, cysts, malignant disease or due to an accessory thyroid gland. Large aneurysms, which may be single or multiple, or an aortitis may occur within the aorta. In the heart congenital lesions, such as valvular disease and dextra cardia, hypertrophy of the heart with or without valvular disease, aneurysm of the heart, or tumors of the heart, myxoma, sarcoma or rhabdomyoma, may occur.

Symptomatology. From the standpoint of symptomatology, pathological changes within the mediastinum vary considerably. The usual picture is that of marked dyspnea, cyanosis, puffy face and neck, with distended veins in the neck and over the thorax. A picture such as this represents an underlying far-advanced pathological process. On the other hand, the processes when first occurring, or even when moderately advanced, may present no symptoms whatever to attract attention to this region, and may be detected merely by a casual fluoroscopical examination. However, most of the cases do present definite symptoms for which the patients seek relief, these symptoms mainly being due to mechanical alteration within the structure involved or mechanical affects on structures adjacent to it.

Pain is the most common symptom of which patients complain. The pain in mediastinal disease may vary greatly in its characteristics. It may be constant, dull, boring in type, or intermittent and stabbing, or knife-like in character. Due to pressure on the intercostal nerves, it may be neuralgic in type, radiating along the course of these nerves. It may also occur over the cardiac area and radiate to the neck and down the arm as an anginoid pain. There may be no pain whatever, but simply a sense of oppression or tightness within the thorax.

Disturbances in the respiratory function are very common, the most frequent disturbance being in the form of dyspnea. This, as a rule, is inspiratory in type and may be persistent or periodic, resembling an attack of asthma. It is a most distressing condition to the patient.

Cough is generally present and varies from an occasional dry cough to the most severe types, and may be either persistent or spasmodic. A cough that is fairly typical is the so-called "gander cough." The cough may be associated with varying amounts of expectoration, amounting in some cases to a definite bronchorrhea. Hemoptysis may occur in some cases, and with a dermoid cyst the patient may expectorate hair.

Secondary changes may occur within the larynx, or because of involvement of the laryngeal nerve causing hoarseness or even complete loss of voice. Disturbances in the action of the heart, such as palpitation, irregularity, precordial pain, cyanosis, syncope and edema may be complained of. There may be difficulty in swallowing, a sensation as though food was sticking in the throat, or the vomiting of foul material when the esophagus is involved. Chills and fever, loss of weight, epistaxis, tinnitus, deafness and vertigo may be secondary symptoms. Occasionally the first thing of which the patient complains is a small swelling coming through the thorax.

Physical Examination. On physical examination of the patient, definite signs may be found pointing to a disturbance within the mediastinum, or through complete lack of signs a definite process within this space may be overlooked. The physical findings in mediastinal disease invariably when present point to the diagnosis of a tumor, except for a few conditions in which more distinctive and characteristic findings are noted. Thus, in the acute inflammatory conditions, in addition to the signs of a tumor, a septic type of temperature and an increased leukocyte count may occur. There may be also redness of the skin overlying a mediastinal abscess. However, pus may be present without these distinguishing features. Also, some of the non-inflammatory conditions, notably Hodgkin's disease, may give rise to definite elevation of the temperature, and, of course, the terminal stages of any of these conditions may do the same thing.

In chronic inflammatory conditions a rough creaking to-and-fro friction sound may be elicited under the manubrium when the arms are moved up and down, as in artificial respiration. Also there may be heard in the right second interspace, close to the sternum, a loud blowing murmur independent of the cardiac cycle and increased by holding the breath and deep breathing. This sign I have never been able to detect.

With mediastinal emphysema the signs are generally characteristic. These are hyperresonance or tympany on percussion and on auscultation, a peculiar tinkling sound will be heard under the sternum in systole and diastole. Should the emphysema be more extensive and invade the superficial tissue of the thorax or neck, one may, of course, feel the "egg-shell" crackling on palpation.

Cardiac lesions also have some rather distinctive findings. Foremost among these findings, of course, are heart murmurs. These are valuable, but heart murmurs may be functional, and murmurs may be produced within the heart due to displacement of that organ.

The location of the apex-beat and the palpation of thrills also are important, as are abnormal pulsations over the thorax, irregular pulse and poor heart sounds. Percussion of the cardiac outline, of course, is very important, but it is very difficult sometimes to determine whether one is percussing the border of the heart or a tumor mass spreading out from the mediastinum.

It is surprising what large aneurysms may exist without presenting any physical signs. Of course, there are found characteristic signs, such as tracheal tug, pulsation of sternum, aortic murmurs, bulging of thorax, unequal pulses and diminished breath sounds over one lung from pressure on the main bronchus.

Excluding the conditions mentioned above, the best evidence on physical examination indicative of mediastinal pathology is brought out on percussion. There may be definite symptoms strongly suggestive of a process in this space, but no conclusive signs can be elicited other than marked dulness or flatness, extending out from the median line further than normally warranted either anteriorly or posteriorly over the thorax.

Secondary changes due to the mediastinal process may be noted in other parts of the body. From pressure on the veins one may get suffusion of the conjunctivæ, staring eyes, cyanosis or lividity of the face, edema of the face, neck and extremities, ascites, pleural effusion, dilated veins in neck and over the thorax, localized edema of the thorax. There may be paralysis of the diaphragm from pressure on the phrenic nerve, paralysis of the vocal cords from pressure on the recurrent laryngeal nerve, inequality of the pupils with dilatation or contraction of the pupil on the affected side from pressure on the sympathetics.

When the attention is focussed on the possibility of an abnormal

condition existing within the mediastinum because of any of the symptoms or physical signs enumerated, the history and physical examination alone may be sufficient to warrant definite diagnoses in some of the cases. A history of trauma to the chest, with or without the penetration of foreign bodies, will immediately bring to mind the probability of a mediastinal hematoma, emphysema or lodgment of foreign bodies there, with resultant abscess formation. A history of an inflammatory process in the lungs or bony thorax, with physical signs in the mediastinal area, will suggest the possibility of abscess formation within the mediastinum. Similarly, a history of malignancy somewhere in the body, with physical signs and symptoms implicating the mediastinum, immediately suggests metastatic involvement.

Excluding the few conditions mentioned previously, it is necessary, in the main, for a definite diagnosis of mediastinal conditions, to rely on other measures than the routine physical examination. Many of these conditions that generally have rather typical signs may occur without showing any of these signs. A most important procedure in the diagnosis of mediastinal conditions is to discover whether or not there is any abnormal condition in other parts of the body. Should one find in association with symptoms and signs, indicating a process within the mediastinum, enlargement of lymph nodes elsewhere in the body, palpable liver or spleen or other abdominal masses, and inflammatory processes within the body, it would help considerably in diagnosing the nature of the mediastinal condition in all probability.

Roentgen-ray Examination. In attempting to locate the structure within the mediastinum involved in the pathological process, the roentgen-ray examination is invaluable, and a few general remarks concerning its application will not be amiss. First of all, while the roentgen-ray may give a shadow indicating a definite abnormal condition present, yet that shadow might not possess sufficient characteristics to enable us to state the tissue from which it arises.

Of course fluoroscopy should always be employed in conjunction with the plate examination, fluoroscopy, if anything, being the more important method to use, as one can view the mediastinum by this method in the various oblique positions, and also can see pulsations if any are present. It is very important to determine whether or not the mediastinal shadow pulsates, as this is generally the distinguishing sign of an aneurysm; but an aneurysm may not pulsate, due to an organized clot being contained within it, while many tumors lying adjacent to the heart and aorta may pulsate, due to transmission of the impulse from the heart. If the aorta is suspected of being the cause of the shadow, and yet the shadow does not pulsate, turn the patient in the oblique positions and trace the aorta throughout its course within the thorax to determine whether or not it is abnormal.

Should a mediastinal shadow be seen on fluoroscopy, before drawing a conclusion as to its location and character, the esophagus should be viewed by means of an esophageal paste. By this method, many pathological conditions will be proven to be occurring within

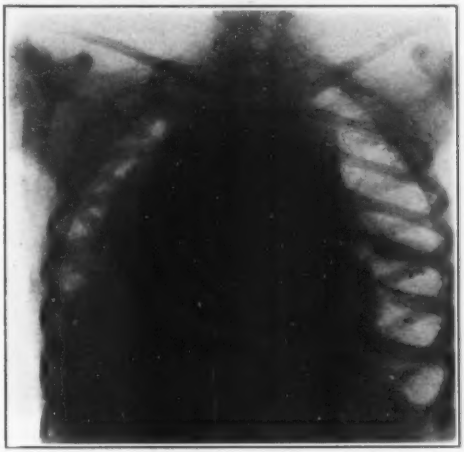

FIG. 1.—Large saccular aneurysm of the ascending portion of the aorta. Shadow showed no pulsation whatever. Because of this fact and its large size and sharply defined borders, case was considered probably a lymphosarcoma. At autopsy a large organized clot about the size of a large grapefruit was found within the aneurysmal sac.

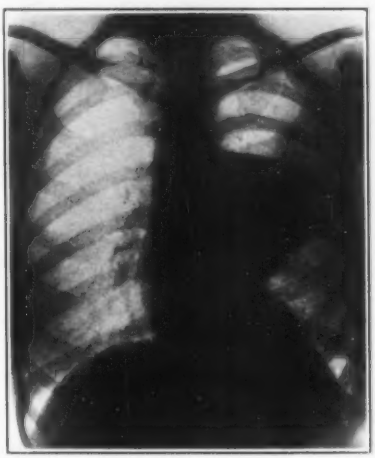

FIG. 2.—Dermoid cyst of mediastinum. Note its triangular appearance due to pressure. Shadow showed a marked transmitted pulsation due to its nearness to heart. Clinically considered a pulsating empyema.

the esophagus, and also many conditions considered to be abnormalities of the esophagus will be seen to be conditions outside of the esophagus pressing on its walls. This method will reveal the

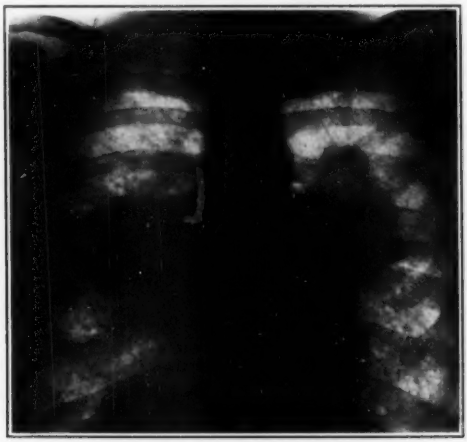

FIG. 3.—Case of pneumoconiosis in a miner, showing marked bilateral involvement of the mediastinal glands.

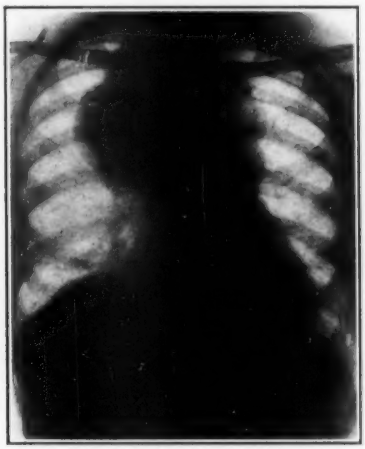

FIG. 4.—Hodgkin's disease of mediastinum, with involvement of the glands mainly on the right side.

diverticula filling-up and then overflowing into the esophagus, the cardiospasm with its marked dilatation of the esophagus, the tracheo-esophageal fistula or esophageal stenosis, or the stricture of the esophagus malignant, syphilitic or traumatic.

Lesions involving the mediastinal glands usually appear as a bilateral mass at either hilus area. Some cases of glandular involvement may, however, be unilateral. A somewhat characteristic

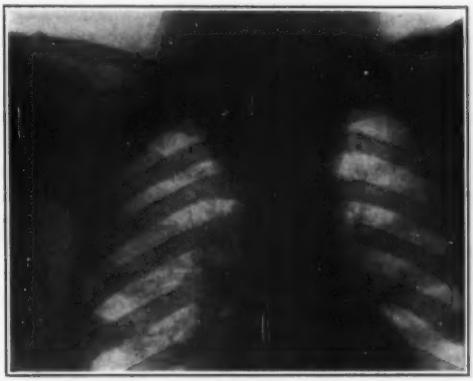

FIG. 5.—Case of substernal thyroid. Note the shadow extending down from the neck sharply defined with its base in the neck.

FIG. 6.—Case of encysted mediastinal abscess following pneumonia. Abscess overlying the heart shadow on the left side. Note its sharply defined convex outer margin.

appearance of glandular masses is that the outer border is scalloped in its outline. Of course the etiology of the glandular involvement is not revealed by the roentgen-ray.

Thyroid enlargements generally appear as a shadow extending down from the neck with its lower border convex downward.

These tumors may also be seen to move with the act of swallowing. Thymic enlargements extend much lower down in the mediastinum than do those of the thyroid and sometimes are of such a large size as to cover a considerable portion of the heart outline. When smaller they are generally seen as a shadow extending out on the right side only.

Of the cardiac conditions, dextracardia and cardiac hypertrophy, many times quite typical of a certain type of valvular disease, are easily recognized. Pericardial effusion may show as an enlargement of the total heart shadow or, if the effusion is encysted, simply as a localized enlargement of the heart area not conforming to any known type of hypertrophy. No definite cardiac pulsation can be detected in the outline of this shadow, and also its outlines may be changed by a change in posture of the patient.

The benign growths are generally unilateral and have no special characteristics except for the chondroma and osteochondroma, which are very dense in structure. The cysts may be very symmetrically rounded in outline but, as a rule, they are not, because of being subjected to pressure effects. They are, however, very sharply defined in outline, and in the case of dermoids may contain teeth or bony structure.

Air within the mediastinum is, of course, quite typical, showing on the plate as a black shadow with no markings of any sort running through it. Foreign bodies also are quite easy of detection if opaque. Occasionally the foreign body is a non-opaque material lodged at the bifurcation of the trachea. This may sometimes be suspected because of an increased aëration of the lung on the affected side.

Fluid within the mediastinum is generally encysted and also generally purulent. In the anterior mediastinum the amount of fluid present may be too small to be seen, as it lies directly in front of the heart shadow which hides it, or if considerable in amount it may bulge out on either side of the heart shadow and become confused with it. In the posterior mediastinal space, or laterally, the shadow of the fluid always is sharply circumscribed, and has one border at least, convex in outline.

The shadows of fluid in the mediastinum at times may very easily be mistaken for tumors. It may be of advantage, should this be the case, to roentgen-ray the patient at different intervals of time, watching the growth of the shadow and any invasive qualities it may possess, in order to diagnose the condition. There remain some of the benign tumors, tumors of the trachea and bronchi and tumors of the nerves, that may all cast shadows on the roentgen-ray plate but do not possess sufficient characteristics to enable one to definitely diagnose their nature.

Bronchoscopy and Esophagoscopy. Further investigations include bronchoscopy and esophagoscopy. With tumors of the bronchus,

even though they are large enough to cast a shadow on the roentgen-ray, bronchoscopy is the only method of definitely proving that the tumor involves the bronchus and not some other structure.

Laboratory Examinations. Other laboratory measures may still be indicated in order to make our diagnosis complete. Thus, in the case of glandular enlargements a blood count may prove a leukemic disease to be present. A blood count may also be of some value in differentiating an abscess from a tumor. An eosinophilia may indicate hydatid disease or make one suspect actinomycosis. A tuberculin test or sputum examination may reveal the glandular condition to be due to tuberculosis. Finally, if there be any superficial glands one may be removed and sectioned for diagnosis. A Wassermann test may occasionally clear up the diagnosis in an unusual case of aneurysm or enlargement of the glands or in the case of a gumma of the mediastinum.

Summary. With detailed and careful examination and knowledge of the procedure involved, a definite diagnosis of practically all mediastinal conditions can be made, with the exception of some of the benign tumors and tumors involving the nerves. Experience, of course, will teach many short cuts to follow in quickly arriving at a diagnosis of the conditions present in this region, without having to perform all of these tests outlined in each individual case.

REVIEWS.

NON-SURGICAL DRAINAGE OF THE GALL TRACT. By B. B. VINCENT LYON, A.B., M.D., Chief of Clinic, Gastro-intestinal Department of the Jefferson Hospital; Attending Physician (formerly Pathologist) to the Methodist Episcopal Hospital. Pp. 640; 175 illustrations and 10 colored plates. Philadelphia and New York: Lea & Febiger, 1923.

IN September, 1919, the author of this new volume had his first paper published, on biliary tract drainage by means of the capillary duodenal tube. Since this date a literature has been developed on the method which is not entirely in accord with the claims made in this original contribution nor with the somewhat modified contentions made in subsequent articles. The method seemed on first thought a most rational one to cope with the difficult problems of gall-bladder diagnosis and therapy but in application by other workers many facts have been developed which seem to somewhat minimize its value. It is therefore of great interest at this time to receive a book from the author's pen; for whatever one may believe about the possibilities of non-surgical drainage of the gall tract, its author deserves much credit for suggesting a diagnostic and therapeutic scheme having potential possibilities. He has put much energy into his work and has shown a genuinely honest enthusiasm.

The book contains thirty-six chapters. Ten of these chapters are devoted to the presentation of fifty case reports, somewhat in protocol style with added discussion and comment. Twelve of these case reports were not under the author's care. Other chapters take up the embryology, histology, anatomy, physiology and chemistry of the hepatic tree. Still others are devoted to various aspects of gastro-intestinal diagnosis, gastric analysis, stool examination, functional liver tests and, of course, one chapter to an abbreviated description of the technic of non-surgical drainage of the gall tract and still another to a more detailed description of the technic. A very good chapter on enzyme activity in the duodenum is contributed by Olaf Bergeim. Kolmer has written part of a chapter on bacteriological technic, Manges has written a chapter on roentgen-ray diagnosis of gall-bladder disease and Cheney one on the clinical differential diagnosis of the same disease. Besides the engraved illustrations and colored

plates, very elaborate forms of various types have been included. These are used by the author in his case records. Adverse criticism of the claims made for biliary drainage, as developed in the volume and previously in the author's articles, would make a large paper in itself. It is sufficient, however, to say that the current literature will supply this for those who may be interested. It may be said fairly that the author has called attention to some exceedingly important points in connection with biliary tract disease. He has started what, we believe, will be very fruitful work in this field. Gall-bladder disease is a most difficult subject and is upon uncertain ground. Conclusions on diagnostic aids and efficacious therapy must be cautiously made. Any methods, however, that offer hope are acceptable. S.

THE AMERICAN ILLUSTRATED MEDICAL DICTIONARY. By W. A. NEWMAN DORLAND, A.M., M.D., F.A.C.S., Member of the Committee on Nomenclature and Classification of Diseases of the American Medical Association. Twelfth edition. Pp. 1296. Philadelphia: W. B. Saunders Company, 1923.

FOR nearly twenty-five years this dictionary has been one of the model dictionaries published in America. It is in all respects an extremely valuable work, as the number of editions and length of time that it has existed shows. In the present new edition the volume has been increased in size by 99 pages by the addition of nearly three thousand new words. The physician who has need of a dictionary, and most physicians do need a new dictionary every few years on account of the large number of new words that are coming into medical terminology, may rest assured that if they purchase Dorland they are securing a volume which is a standard and thoroughly satisfactory from their standpoint. M.

FOOD FOR THE DIABETIC. By MARY PASCOE HUDDLESON, Consulting Dietitian. Pp. 75; 2 illustrations. New York: The Macmillan Company, 1923.

Food for the Diabetic was written for the patient, to be used by him as a guide to the control of the diet as well as to indicate to him methods of preparation of attractive diabetic food. This small volume will be of great assistance to the physician if it is placed in the hands of his diabetic patients. It not only deals with diet, but also gives very sensible directions as to the general care of the diabetic patient himself. M.

LEHRBUCH DER GRENZGEBIETE DER MEDIZIN UND ZAHNHEILKUNDE. Edited by DR. JULIUS MISCH, Berlin, in collaboration with numerous authorities. Third edition. Two volumes. Pp. 1382; 596 illustrations, many in colors. Leipzig: F. C. W. Vogel, 1923.

THE fact that the third edition of this work has appeared within a few months after the second is sufficient evidence of its popularity in Germany. In it is presented all of the information about diseases of the body as a whole deemed necessary in the education of the dentist as a mouth specialist, and, on the other hand, the internist as well as specialists in various fields will find here a very complete description of the mouth symptoms of different general diseases. The subject is dealt with in turn from the standpoint of the internist, the pediatrist, the neurologist, the syphilographer, the dermatologist, the gynecologist, the otolaryngologist, the ophthalmologist, and the specialist in industrial diseases. With this arrangement a good deal of repetition is necessarily unavoidable, adding considerably to the bulk of the volumes. It is evident that less importance is ascribed in Germany to oral foci of infection as causative factors in arthritis and other conditions than in America. Perhaps the most commendable section is that concerning the manifestations of industrial diseases in the mouth. To obtain the information here collected in one volume one would ordinarily have to search an entire library. The illustrations, many of them in colors, could hardly be excelled. It is a matter for regret that there is no such work as this in the English language. I.

GRUNDRISS DER INNEREN MEDIZIN. By DR. A. VON DOMARUS, Director of the Medical Division of Auguste Victoria Hospital, Berlin-Weissensee. Pp. 640; 58 illustrations. Berlin: Julius Springer, 1923.

CALLED an "Outline" this book is virtually a text-book on medicine, covering the field almost as fully as the standard one-volume English works. The subject matter is well presented and with few exceptions (*e. g.*, insulin in diabetes, sensitization in asthma, electrocardiography) is adequate and up to date. The reviewer was particularly impressed by the physical characteristics of the book. A handy, simply-bound medium octavo of 640 pages with compact but clear and pleasing print, the volume is just an inch thick and weighs 2.5 pounds (in contrast to the one-volume English texts that average over 4 pounds). A similar make-up might be recommended to American publishers: a text-book could be sold for half the present rates—smaller initial profit, but far more likely to "repeat" in new editions. K.

APPLIED PSYCHOLOGY FOR NURSES. By DONALD A. LAIRD, Assistant Professor of Psychology, University of Wyoming. Pp. 236; 49 illustrations. Philadelphia: J. B. Lippincott Co., 1923.

THE selection of subjects which the book presents is admirably suited to the work of nursing. The arrangement is very good indeed but the amount of material given under the themes is wholly inadequate to teach them successfully to girls who are entering into the field of nursing. A book covering as many subjects as these must be considerably extended in order that the subjects will be taught; as it is, the book is neither a dictionary nor a text. It should be either one or the other. B.

DIATHERMY AND ITS APPLICATION TO PNEUMONIA. By HARRY EATON STEWART, M.D., Attending Specialist in Physiotherapy, U. S. Marine Hospitals, N. Y., Director, New Haven School of Physiotherapy. Pp. 210; 45 illustrations. New York, Paul B. Hoeber, 1923.

THIS volume is a short description of diathermy technic together with an account of its application in the treatment of pneumonia. The author is enthusiastic about this treatment, but of course it is impossible to draw conclusions from 67 cases of a disease such as pneumonia which varies so in severity of symptoms in different individuals and in the virulency of the disease at various times.

M.

CLINICAL LABORATORY DIAGNOSIS. By ROGER SYLVESTER MORRIS, A.B., M.D., Professor of Medicine in the University of Cincinnati and Director of the Medical Clinic of the Cincinnati General Hospital. Pp. 456; 99 illustrations. New York, D. Appleton & Co., 1923.

A BOOK on clinical laboratory methods and diagnosis which is designed for the use of students and practitioners of medicine as is this book should fulfil several requisites. It should be convenient in size; the directions should be clear and terse; the methods of performing the various tests should be those that have been proven by actual use to be practical and valuable; it should be written by one who is experienced in the actual manipulations and performances of the tests, and, lastly, in order to correlate the laboratory diagnosis with the clinical it should contain a certain amount of clinical data. All these requisites are found in this new volume by Dr. Morris. In addition to the clear-cut presentation of the subject it might be

added there are several features that are particularly of value. In the first place the references are well given and there is also an index to the authors as well as an index of subjects. There is a splendid table on normal and pathological blood chemical analyses. Pathological blood conditions are classified, for example, twenty-three causes of lymphocytosis, seventeen causes of mononucleosis and so on. And lastly the illustrations are well selected, while those of the blood are particularly good, the author being the artist. Dr. Morris is to be congratulated upon his work. The reviewer feels confident that he can predict for it a long life and great popularity.

M.

INTERNATIONAL CLINICS. Volume IV, 33d Series, 1923. Pp. 308. Philadelphia: J. B. Lippincott Company, 1923.

DR. THAYER has a most interesting contribution in the present number of *International Clinics*. There is also a splendid symposium on gastrointestinal ulcers, a most interesting review on otology for the medical student by Dr. Randall as well as the Alvarenza Prize essay of the College of Physicians of Philadelphia for the year 1923 on Echinococcus Disease. In addition to these outstanding contributions there are more than a dozen other articles on surgery, pediatrics, diagnosis, etc.

M.

THE MEDICAL DEPARTMENT OF THE UNITED STATES ARMY IN THE WORLD WAR. VOLUME V. MILITARY HOSPITALS IN THE UNITED STATES. Pp. 857; 204 illustrations. Washington: Government Printing Office, 1923.

THE fifth volume of the governmental history of the Medical Department in the World War is a large volume upon the various types of hospitals, such as were built in this country to supply cantonments, embarkation camps, ports of debarkation, etc. Every type of hospital and every hospital that was constructed or provided for in this country is given more or less detailed mention in the book with particular reference to the base hospitals at the various camps. For each of these hospitals statistics are given concerning the number of sick and wounded that were in the hospital during the various months they functioned and the personnel on duty, as well as a one- to four- or five-page description of the general plan of the hospital. The book is teeming with interesting data; of particular interest from the medical viewpoint is to review statistically the frightful toll that influenza took among the soldiers of this country. For

example, at the Base Hospital at Camp Sherman, Chillicothe, Ohio, commanded by Lt.-Col. Kinard in the month of October, 1918, there were 1056 deaths, the month preceding that there were 28 and the succeeding month 31 which was about the average monthly death-rate in the hospital. The same figures held in about the same proportions in many of the camps throughout the country. This fifth volume is as well presented as the first volume, intervening volumes have not as yet appeared. M.

NEUROLOGIC DIAGNOSIS. By LOYAL E. DAVIS, M.D., Associate Professor of Surgery, Northwestern University Medical School; Fellow of the National Research Council. Pp. 173; 49 illustrations. Philadelphia and London: W. B. Saunders Company, 1923.

THIS short work is an effort to correlate the basic principles of anatomy, physiology and pathology of the central nervous system with the clinical manifestations of disease. The first 62 pages are devoted to a brief consideration of the first mentioned factors, while the remaining 100 pages are devoted to a discussion of illustrative cases, which are well presented, easy to read and in every way extremely instructive. The book should prove of very definite value to the student and internist. M.

FIGHTING FOES TOO SMALL TO SEE. By JOSEPH MCFARLAND, M.D., Sc.D., Professor of Pathology in the Medical Department of the University of Pennsylvania. Pp. 309; 64 illustrations. Philadelphia: F. A. Davis Company, 1924.

"THE war gave us a new word—'Preparedness,'" says the author of this work in his introduction. "Many have insisted that preparedness implies a state likely to be dangerous through the temptation to aggression. In the preparedness against epidemic disease the only aggression is against inhuman foes, from whom we can want nothing, and can take nothing, but by whom we may be invaded, devastated and depopulated. We must fight these foes too small to see." While the book deals with subjects unfamiliar to the average reader, it is written in a way admirably calculated to make him familiar with things of the highest importance to his life and health. The text, which had its beginning in four lectures delivered at the Wagner Free Institute of Science of Philadelphia, is divided into seven chapters, dealing, respectively, with the

Origin of Microörganisms, the historic error concerning the Spontaneous Generation of Life, Effects of Microörganisms, Infection, Transmission of Causes of Disease from Individual to Individual, Prevention of Disease through Increase of Resisting Power and Prevention of Diseases Transmitted by Insects. Sixty-four engravings enhance the popular appeal of the work and its beneficent purpose in dissipating the all too prevalent ignorance of the causes and modes of transmission of diseases, and in combating that apathy and prejudice against new measures which are the chief obstacles to the extinction of infectious diseases.

Especially valuable from the every-day point of view is the author's treatment of such themes as dangers in milk and water; infection from vegetables; efficient and inefficient vaccination; preventing diphtheria; ticks, lice and bedbugs. Much of the concluding portions of the book is devoted to interesting summaries and selections from historic accounts of the plague, or black death, from Gould and Pyle's *Anomalies and Curiosities of Medicine*, Pepys' and Evelyn's *Diaries*, and Boccaccio's account of this malady. There are also detailed descriptions of the latest discoveries in regard to the origin and treatment and prevention of the African sleeping sickness. W.

How Our Bodies are Made. By R. M. Wilson, M.B., Ch.B. Pp. 246; 118 illustrations. London: Henry Frowde, Hodder & Stoughton, 1923.

This is an extremely practical and most interesting explanation of physiology for young people and could be very readily used for instruction in elementary schools. M.

Problems in Tuberculosis. By Sir James Kingston Fowler, K.C.V.O., C.M.G., M.A., M.D., D.Sc. (Hon.), F.R.C.P., Consulting Physician and Emeritus Lecturer on Medicine, The Middlesex Hospital; Consulting Physician to the Brompton Hospital for Consumption and Diseases of the Chest and to King Edward VII Sanatorium. Pp. 64; 1 illustration. London: Oxford Medical Publications, 1924.

The author has written down here the results of many years of close study of tuberculosis. He presents his impressions in the interesting and rather chatty way which is so attractive in the average English text-book. The book will well repay reading by the internist. M.

PROGRESS
OF
MEDICAL SCIENCE

SURGERY

UNDER THE CHARGE OF

T. TURNER THOMAS, M.D.,

ASSOCIATE PROFESSOR OF APPLIED ANATOMY IN THE MEDICAL SCHOOL AND ASSOCIATE PROFESSOR OF SURGERY IN THE SCHOOL FOR GRADUATES IN MEDICINE IN THE UNIVERSITY OF PENNSYLVANIA; SURGEON TO THE PHILADELPHIA GENERAL AND NORTHEASTERN HOSPITALS.

Roentgenological Diagnosis of Cholecystic Disease.—CARMAN, MACCARTY and CAMP (*Jour. Radiol.*, 1924, **2**, 80) say that it has been impossible to differentiate the roentgen-ray densities of normal and abnormal bile. There is no apparent reason why the normal gall-bladder should not cast a shadow as often as the diseased organ. Various observers have described certain indirect signs of disease of the gall-bladder consisting of deformities of the antrum of the stomach, duodenal cap and second portion of the duodenum supposedly produced by a distended gall-bladder, and certain spastic phenomena, pylorospasm, delayed motility and cardiac regurgitation. Leonard asserted that direct signs are present in but one-third of the cases and that two-thirds of his diagnoses are based solely on indirect signs. In a large series of 343 cases positive report of disease was made in 52.9 per cent and negative diagnosis in 44.6 per cent, when there was evidence of mild or extreme grades of disease. The study of these cases raises the question whether the results warrant the time and expense required for roentgenological examination. All the gall-bladders removed at operation were examined by the pathologist and found to be diseased. The accuracy of roentgenological examination is therefore limited to 50 per cent.

Studies of the Exophthalmic Goiter and the Involuntary Nervous System.—HYMAN and KESSEL (*Arch. Surg.*, 1924, **8**, 149) remark that the present study was upon the course of the subjective and objective manifestations in 50 unselected patients observed over a period of two years, in whom no specific measures were instituted. It was noted that in the vast majority of the patients with exophthalmic goiter there was a marked and progressively increasing tendency toward "spontaneous" recovery. Recovery was not complete in the sense

of cure, but was marked by the persistence of residual subjective symptoms. In at least the first two years of the remissions the occurrence of severe incapacitating exacerbations were infrequent. These results of "skilful neglect" compare favorably with the results of specific therapeutic measures.

The Immediate Effect of Subtotal Thyroidectomy in Toxic Goiter.—SEGALL and MEANS (*Arch. Surg.*, 1924, **8**, 176) say that the early effects of operations amounting to subtotal thyroidectomy in patients with toxic goiter are a rise in basal metabolism and pulse, which can be largely explained on the basis of fever and emotion. A progressive fall in metabolism and pulse brings them within normal limits in from four to twelve days. The rate of detoxication following subtotal thyroidectomy is quite similar to that during the period of recovery from hyperthyroidism induced by thyroid feeding. While pulse and basal metabolism show considerable parallelism, the latter fluctuates less and is the better index of the degree of hyperthyroidism.

The Clinical Diagnosis of Carcinoma of the Breast.—BATTLE (*Lancet*, 1924, **1**, 206) states that the swellings which it may be difficult to distinguish from early carcinoma of the breast are cysts, fibroadenomata and chronic inflammation. When the cysts and fibroadenomata are associated with local inflammation the diagnosis becomes at times impossible. Sometimes a simple cyst bursts through overstretched skin and a fungating sore develops. It is advisable to explore small swellings (especially after the age of thirty years) about which there is doubt. Exploration should show even in small malignant ones, a cartilaginous resistance to the knife, a hard edge, a cupping of the surface on which there is the appearance of the unripe pear. This picture should not be confounded with anything else. A mistake between tuberculous deposit and carcinoma is not usual in the first stage. The local enlargement is insidious and little may be noticed to cause alarm until suppuration ensues. Some sarcomata develop cartilaginous change and so resemble hypertrophic carcinoma in their unusual hardness, but they are usually of more rapid growth. Characteristic invasion of surrounding parts is absent and the hardness is mostly distributed in an irregular manner.

The Selection of Patients and of Operation in the Surgical Treatment of Pulmonary Tuberculosis.—LILIENTHAL (*Am. Jour. Surg.*, 1924, **34**, 1 and 2) says that surgery is not intended to supplant medicine in the treatment of tuberculosis of the lungs. It should be resorted to when medical and hygienic treatment have nothing more to offer and the patient's life is intolerable or the prognosis is grave. Operation may have two distinct objects—placing at rest the entire lung and secondly the obliteration of apical cavities. Collapsing thoracoplasty with phrenic nerve resection puts the lung at rest to a greater degree than is possible by any other known method. It is only to be applied when the other lung can function sufficiently to support life and when it is not affected by rapidly developing tuberculosis. Thoracoplasty does not take the place of therapeutic pneumothorax for no return of function is possible. In pneumothorax lung function can

be restored, when desirable, in a large number of cases. Arrest or great improvement following collapsing thoracoplasty may be expected in about 75 per cent of the cases. The obliteration of apical cavities can be performed on both sides of the chest and is worth performing when the disease in the remaining parts of one or both lungs is capable of arrest.

Prognosis in Giant-cell Sarcoma of Long Bones.—COLEY (*Ann. Surg.*, 1924, **79**, 321) says that various names have been given this tumor, beginning with tumor *a* myeloplaxes, myeloid sarcoma, giant-cell sarcoma, benign giant-cell sarcoma of the epulis type, giant-cell tumor of Bloodgood, osteitis fibrosa cystica (von Recklinghausen), hemorrhagic osteomyelitis (Barrie). The author's series of 50 cases shows that the disease had existed less than six months in 50 per cent of the cases and more than a year in only 6 cases. The upper end of tibia, lower end of radius and lower end of femur are the most frequent sites. The lower jaw is the most frequent site of other bones. The growth gradually expands the bone, destroying the bone slowly by absorption, but rarely breaking through the periosteum, and still more rarely invading a neighboring joint. The author believes a certain number of these tumors are definitely malignant and cause death by metastases, and that it is not always possible to differentiate the benign from the malignant, especially in the early stages of the disease. There is no uniform method of treatment in giant-cell sarcoma. Immediate amputation is seldom done at present. Curetting with the application of carbolic acid is probably more largely used than any other method. Ewing would give up curettage entirely and substitute routine treatment with roentgen-ray and radium.

Paget's Disease of the Female Nipple.—BLOODGOOD (*Arch. Surg.*, 1924, **8**, 461) states that the evidence would suggest that ultimately cancer develops in every ulcer of the nipple. The moment cancer develops in the ulcer of the nipple there may be infiltration of the cancer cells along the ducts. In 13 cases of early cancer of the nipple in only 2 were the ducts free from any evidence of cancer. In only 4 of this series was the author able to demonstrate nests of cancer in the lymphatics of the breast. This is evidence of the danger of any unhealed lesion of the nipple and also clearly demonstrates that there is but one operation for cancer of the nipple, no matter how early, and that is complete operation. The age of the patients with cancer of the nipple has varied from thirty-eight to eighty-four years. The larger number of patients were past the menopause. So far none have been in colored women. The author's whole evidence is against excision of only the breast. It is unnecessary when the lesion is benign, and not sufficient when the lesion is malignant. When Paget's disease is seen in its latest stages it is apparently hopeless from the standpoint of any treatments.

Diseases of the Colon.—CARMAN and FINEMAN (*Jour. Radiol.*, 1924, **1**, 129) say that the barium enema has been found of greater value than the ingested meal in the diagnosis of diverticulitis, neoplasms, tuberculosis and chronic ulcerative colitis. Antispasmodics in physio-

logical doses are made use of in cases in which spasticity is present. A non-retention of the barium in the ceco-colon shortly after its filling with the bariumized mixture has been observed in carcinoma, tuberculous and chronic ulcerative colitis. Frequently lesions cannot be detected unless deep palpation and approximation of the bowel walls is resorted to during fluoroscopical examination. Motility has been found of very limited value in the diagnosis of colonic disease. Very small lesions, the extent of the lesion and lesions in the distal half of the colon can usually be best demonstrated with the barium enema. Roentgenological diagnoses of diseases of the colon should, as a rule, be limited to actual shadow phenomena observed—a final diagnosis must be based on a correlation of all known data. A specific diagnosis cannot be made with assurance until a biological examination of tissue removed at operation has been made.

A New Mercurial for the Intravenous Treatment of Syphilis.—SNODGRASS (*Lancet*, 1924, **206**, 117) states that this mercurial has been given the name of "flumerin," containing 33 per cent of mercury in the non-ionized form. Gross secondary lesions show material alteration in the direction of healing within one week as a result of the administration of flumerin alone. No other mercurial preparation would appear to produce marked changes so rapidly. The action is not lasting, however. Relapses in secondary cases may occur within a relatively short time or even while treatment by flumerin is being continued. A positive Wassermann reaction is usually not altered to a negative one. In this respect flumerin does not compare unfavorably with an equivalent use of other mercurials given without arsphenamin preparations. Tertiary cases which present definite lesions show rapid clinical improvement with flumerin alone. The rapidity appears much greater than that produced by other mercurials, but less than by the combined treatment by mercury and iodides. Extended trial of flumerin should be made on account of its rapid antisyphilitic effect. This rapidity is its outstanding property.

PEDIATRICS

UNDER THE CHARGE OF

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Meningeal Hemorrhages in the Newborn and Their Remote Consequences.—GORDON (*Am. Jour. Dis. Child.*, 1924, **27**, 303) says that the cause of meningeal hemorrhage is principally the tearing of the membranes due to their overstretching, which leads to the rupture of the bloodvessels. To produce a tear there must be great cranial stress. Since the latter is often the result of protracted, difficult labor, with instrumental delivery, the obstetrician should bear in mind that

the force used in the application of the forceps should not be excessive, or should not be applied in the wrong diameter of the head, as, for example, the antero-posterior diameter. In the latter case the vertical elongation of the head is more liable than anything else to cause overstretching and tearing of the meninges. Forceps are useful and in many instances have been responsible for the saving of lives, but they may also be responsible for injuries in the fetus leading to consequences that have a direct bearing on the later physical and mental development of the child. With a certain degree of possible errors, supratentorial hemorrhages present a somewhat different clinical picture from the infratentorial type. In the former the blood spreads over the hemispheres of the cerebrum; in the latter over the hemispheres of the cerebellum but also into the medulla. In the former the blood cannot go beyond the lower surface of the tentorium; in the latter the blood reaches the subarachnoid spaces, and may extend into the spinal canal. For these reasons in the supratentorial hemorrhages at birth there is found a bulging fontanelle and a group of nervous phenomena, such as sleeplessness and great restlessness and convulsive seizures with a continuation of the condition. In infratentorial hemorrhage there is considerable depression, apathy, somnolence, early cyanosis, vasomotor and respiratory manifestations and rigidity of the neck muscles. In view of the anatomical differences, respiratory and other bulbar disturbances will not be observed in the supratentorial cases. For anatomical reasons in infratentorial cases lumbar puncture may be of considerable benefit. In the supratentorial cases lumbar puncture does not avail much as the blood cannot reach the subarachnoid easily. Surgical therapy is almost the only issue. Early craniotomy is definitely indicated. Favorable results can only be expected when the operation is performed within a few days of birth. After the clot has already produced damage to the cortical tissue no relief can be expected. It seems logical that in all cases indicating increased intracranial pressure at birth lumbar puncture should be resorted to at once, before a definite localization is made, since in the infratentorial group it is of definite therapeutical value and in the supratentorial the diagnosis may be promptly established.

Convalescent Whole Blood Plasma and Serum in Prophylaxis of Measles.—ZINGHER (*Jour. Am. Med. Assn.*, 1924, **82**, 1180) found that convalescent measles serum, plasma or whole blood, had definite value in the prophylaxis of measles. It can be used to produce complete passive immunity if injected within the first four or five days after exposure, and a mixed form of immunity if injected in larger dose after the fifth day. It can be injected in small doses after the fifth day of exposure to modify the character of the disease, rather than to prevent its development. If such an attack develops the immunity will probably be permanent. The blood plasma or serum of recovered cases, such as that from brothers and sisters, and also of adults that have had measles in childhood, can replace convalescent serum if used in large amounts. With the increasing number of days since exposure larger doses of convalescent doses have to be used when it is desired to produce complete immunity. The dose of serum during the first days of exposure is 2.5 cc; during the fifth and sixth days 5 cc, and during

the seventh to eighth days 7.5 cc. To influence the type of measles so that a modified type of the disease will develop, the dose is from 2.5 to 3 cc from the fifth to the tenth day after exposure. These doses are calculated for children three years of age. They should be proportionately higher for older children and adults. A quick, convenient and simple way, which can be used with ease both in hospital and in private practice when prepared convalescent serum is not available, is to inject intramuscularly whole blood, citrated or non-citrated, in double the amounts recommended for the serum. Complete passive protection with convalescent serum or plasma has its field of usefulness in protecting the very young and feeble children and those suffering from rickets, tuberculosis, diphtheria and whooping-cough. Also during the cold seasons of the year, when catarrhal conditions prevail and there is danger of pulmonary complications, such extreme immunization is often indicated. In private practice in dealing with normal healthy children who have been exposed to measles, as well as in some institutions taking care of healthy robust children, it will be generally more desirable to use convalescent serum, the serum of recovered cases or adult serum, so as to obtain a modified and mild form of the disease. A fairly permanent immunity will thus be established, rather than a temporary protection for a short time. In certain institutions, foundling asylums and hospitals the indications are to stamp out the outbreak of measles, completely protecting the exposed and non-immune children with convalescent serum. Outbreaks of measles cause a high mortality among these children and cripple the institution badly. The history of previous attacks of measles should carefully be inquired into and recorded for each child admitted to the hospital or institution. Such records will greatly simplify subsequent immunization work with convalescent serum. A supply of convalescent serum of plasma can be obtained and kept on hand if coördinated efforts are made between physician and health authorities. The supply is bound to remain limited. The great value of recovered serum or of adult serum consists of the ability to obtain it from parents or other relatives. Of 102 non-immune children injected after exposure to measles for varying lengths of time, 92 were completely immunized, 7 developed modified measles and 2 developed typical measles. Of these 2 only 1 child was injected before the fifth day of exposure. One child was protected for twenty-eight days, but developed measles after a second exposure. Of 58 additional children injected in two institutions 23 developed mild measles and 4 developed typical measles. These 4 children were injected with 3 cc of a thirty-five-day convalescent plasma. A large dose of this or a smaller dose of a more recent convalescent would most probably have prevented the development of typical cases. Of 37 control children who were not injected 7 developed typical measles and only 3 a mild form.

Studies on the Acidity (Hydrogen-ion Concentration) of Infants' Stools.—TISDALL and BROWN (*Am. Jour. Dis. Child.*, 1924, **27**, 312) describe in this paper a simple procedure for determining the hydrogen-ion concentration of infants' stools. In this investigation 1300 determinations were made. The hydrogen-ion concentration from normal newly born babies fed from the mothers' breasts was found to be

singularly constant, varying from 4.7 to 5.1. The acidity of stools from artificially fed infants was found to vary from pH 4.6 to somewhat more alkaline than pH 8.3. An acidity as great as pH 4.6 was encountered in artificially fed infants only in severe diarrheal conditions. Infants fed on butter-soup, cows' milk dilutions with added carbohydrates, and whole soured milk with added carbohydrates, generally had stools more alkaline than pH 7. Whole soured milk with added carbohydrates up to a total content of 20 per cent generally produced strongly alkaline stools. No difference was consistently noted in the acidity of the stool, whether the added carbohydrate was in the form of corn syrup, dextrimaltose or cane sugar. The effect produced by other sugars was not determined. The degree of acidity of the stools was generally increased by the presence of parenteral infections. Based on this work and the work of others, the factors which influence the acidity of the stools have been considered. From the chemical standpoint the acidity apparently depends on the ratio, in the intestinal zone of fermentation, of the carbohydrate on the one hand to the protein and base on the other. The amount of carbohydrate in the zone of fermentation apparently is influenced by the extent of the zone of fermentation, by the type of carbohydrate and by the state of health of the intestinal cells.

A Comparison of the Metabolism of Some Mineral Constituents of Cows' Milk and of Breast Milk in the Same Infant.—WANG, WITT and FELCHER (*Am. Jour. Dis. Child.*, 1924, **27**, 352) found that, owing to failure completely to evacuate the bowels every twenty-four hours, accurate determinations can be secured only from the average values of at least a three-day period. A change from breast milk to cows' milk, or *vice versa*, was invariably accompanied by a change in the quantity of calcium excreted in the feces. The actual quantity was always greater on a diet of cows' milk. The difference in the calcium excretions of the same child ranged from 0.0726 to 0.7829 gm., with an average of 0.4364 gm. The difference in the calcium excretion in the urine brought on by a change in the diet is slight and inconsistent. Calcium absorption and retention run closely parallel, since the variation in the urinary calcium output is slight and of little significance. The actual quantity of calcium absorbed and retained is greater for cows' milk than for breast milk, but percentage utilization and retention is greater from breast milk, except for older children. With cows' milk the average utilization is 0.7094 gm. per twenty-four hours, and with breast milk 0.4433 gm. The percentage utilization of cows' milk is 47.5 and of breast milk is 63. The figures for calcium retention show an average of 0.8025 gm. per twenty-four hours for cows' milk and 0.4524 gm. for breast milk, or a percentage retention in cows' milk of 46.1 and for breast milk 60.9. The calcium metabolism of breast milk is independent of the age of the child, but that of cows' milk shows a distinct increase with the age of the child both in individual cases and in the group of subjects. The percentage utilization and retention of calcium of breast milk in infants from 1.4 to 5.7 months falls within a range of 10 per cent. In case of cows' milk with children from 0.4 to 6.1 months there is a range of 27 per cent in utilization and 28.4 per cent in retention, the higher figures occurring in the older children.

Arsenic in Human Milk after Intravenous Injections of Arsphenamin.—Fordyce, Rosen and Myers (*Am. Jour. Syph.*, 1924, **8**, 65) examined seventy-five specimens of milk taken from twelve nursing mothers under treatment for syphilis. It was found that after intravenous medication with the arsenicals breast milk shows definite amounts of arsenic after various intervals corresponding in some individuals to the amounts found in the blood of treated individuals after the same lapse of time. The presence of arsenic in mother's milk is more constant than in either the blood or urine, and is found in appreciable amounts long after its administration. The deduction is made that a suckling probably receives sufficient arsenic in its daily feedings to be of some therapeutic value. For this reason the energetic treatment of syphilitic mothers during lactation is advisable.

OBSTETRICS

UNDER THE CHARGE OF

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Pregnancy after Bilateral Amputation of the Breasts.—Schneider (*Monatschr. f. Geburtsh. u. Gynäk.*, 1923, **64**, 295) reports the case of a woman, aged thirty-seven years, in her second pregnancy, who had been in the tropics where she had contracted a parasitic disease, in the course of which hardened areas had appeared in both breasts, for which they had been removed. When aged thirty-six years a pregnancy occurred during which she complained of irregularity of action of the heart, acidity and at times vomiting. During the later portion of pregnancy there was a yellowish discharge. No evidence of syphilis or gonorrhea was present. The patient was brought into the hospital in labor. She was intensely nervous and over the anterior surface of the chest were large scars where the breasts had been removed. The knee-jerks were exaggerated but other reflexes were normal; the urine was normal. Labor proceeded spontaneously and a well-developed child was born. The puerperal period proceeded normally and the patient was discharged in good condition. The case is interesting in view of the fact that it is commonly supposed that there is a close relation between the development and functions of the mammary glands and the uterus; furthermore, it is known that mammary glands and ovaries act in reciprocal relation. It is interesting to observe that this case proceeded normally and that the only variation from a perfectly natural process, was the inevitable failure of breast milk in the nourishment of the child. The infant lost weight after birth to a considerable extent, but was finally well-nourished by artificial feeding.

Hemolytic Streptococci in Pregnancy.—KANTER and PILOT (*Surg., Gynec. and Obst.*, 1924, **38**, 96) review the literature concerning the presence of streptococci in the vaginal secretions during pregnancy. The percentage in which these germs have been found by various observers varies from 4 to 40, and in these tabulations no effort is made to distinguish between hemolytic streptococci and others of the same group. During pregnancy the hemolytic streptococci vary from 2.5 to 50 per cent in cases examined by different investigators. Various explanations have been given for this discrepancy; some allege that it depends upon the manner in which the cultures were taken; others that the general condition of cleanliness in the body of the patient had much to do with the presence or absence of these germs. The idea that all hemolytic streptococci are virulent is not tenable at the present time. Some of the most recent observers believe that it is impossible to differentiate between streptococci existing in the lochial discharge in harmless form, and those causing infection. The writer studied 96 patients, among whom 19 had profuse vaginal discharge during pregnancy, 67 a moderate discharge and 10 had none. There were 19 abnormal and 67 of what might be termed average discharge. Three cultures were obtained—one from the lateral wall of the vagina after separating the labia, the second from the posterior fornix and the third from the os uteri. In obtaining the two latter a sterile speculum was used; the swabs so innoculated were brought in contact with an infusion of agar, to which defibrinated human blood was added—1 part of blood to 1 of agar. Readings were made at the end of twenty-four and forty-eight hours. The germs found were further identified by various forms of culture, and in some cases these were injected into rabbits. From these tests it is interesting to note that these bacteria appear less virulent than streptococci found in the tonsils and nasopharynx of patients. As to the source of these streptococci they evidently were present in the vagina before labor or were introduced by the hands or instruments of those who attended the patient, while some of them undoubtedly came from the throats of attending physicians and nurses, and in some cases the focus of infection was located in the throat, nose or sinus of the patient herself. These observers found the hemolytic streptococci rarely present in the normal vagina and believe that hemolytic streptococci infections arise from without the body of the patient. Droplets of secretion from the throat and nose of attendants and patients are usually conveyed into the bodies of patients by examination and operation, and these droplets often contain hemolytic streptococci. Sneezing or coughing by operators or attendants during an obstetric operation or delivery may also convey germs to the patient, for it has been shown that a normal throat contains hemolytic streptococci in practically 100 per cent of individuals. If a sore throat is present the streptococcus has added virulence and is more dangerous to the pregnant woman. It is also true that the patient's own throat may furnish pathogenic organisms leading to hemotogenic infection of the genital tract. A reasonable precaution in conducting labors would be for attendants and nurses to wear a gauze face mask, to exclude from delivery rooms persons having a sore throat and to isolate all patients who develop a streptococcic sore throat. These researches call atten-

tion to the familiar fact that manipulation of the birth canal or examination or operation increases the possibility of infection.

The Transmission of Arsenic from Mother to Fetus.—The question as to the passage of drugs and various substances from mother to child has always been of considerable practical interest. UNDERHILL and AMATRUDA (*Jour. Am. Med. Assn.*, 1923, **81**, 2009) have reviewed the literature of the subject, finding that there are two antagonistic theories concerning placental transmission. One is that the chorionic epithelium takes a specific vital part in interchanges which occur in the placenta. The other theory considers the chorionic epithelium as a passive membrane whose action conforms to the laws of osmosis and diffusion. The discovery of enzymes in the placenta supports the vitalistic theory. Many of these enzymes have to do only with the living process of the cell in which they are found. Others state that placental transmission cannot be explained merely by mechanical laws because there is a greater concentration of the sodium and potassium salts in the fetal than in the maternal blood. Perhaps the majority of opinion is in favor of the mechanical theory of placental osmosis and diffusion. We know that nutritious material and oxygen pass from mother to fetus and waste products from fetus to mother. Various substances have been proven to pass through the placenta. These have been divided into those soluble in water and diffusible and those insoluble in water and not diffusible, which do not transverse the placenta. If the blood of the mother and fetus at the time of delivery is examined, the result strengthens the mechanical view; there is the same average of uric acid, creatin in the same concentration in maternal and fetal blood, the urea and non-protein nitrogen are the same, the percentage of sugar is slightly lower in fetal blood at the time of delivery. On the other hand, an excess of amino-acid appears in favor of the fetus. It has been shown that fetal and maternal blood are under the same osmotic pressure. Toxins, antitoxins and other products readily pass through the placenta in the same concentration. The mother's blood contains more non-diffusible fats and colloids than does the fetal. In the syncytium, iron, fat and albuminous substances undergo radical changes before entering the fetal circulation. The writers experimented upon animals by injecting neo-arsphenamin intravenously. These experiments show that arsenic is stored up in the placenta and maternal liver as contrasted with fetal tissue. Arsenic is transmitted through the placenta in small quantities, but evidently it is not stored in the fetal tissues which is a fact of considerable clinical importance. This would indicate that the drug can safely be given to pregnant women in the treatment of syphilis in the ordinary doses given to man and non-pregnant women without danger of injury to the fetus. It is a clinical observation that antenatal treatment of syphilis is efficient for the fetus. This seems to be due to the fact that arsenic can act in greater concentration on the spirochetes in the placenta where the drug is stored after serial injection, the drug has a more direct access to the spirochetes in the placenta, owing to the greater vascularity of this organ. The writers found that arsenic is detected in small traces in the fetal tissues after the intravenous injection of neo-arsphenamin into the maternal cir-

culation. The amount of arsenic recovered from the fetal tissues does not increase in proportion to the number of injections given. The drug is stored in the maternal liver and placenta increasing with the number of doses given.

The Prophylactic Treatment of Eclampsia by Artificial Light.—HOCKENBICKLER (*Monatschr. f. Geburtsh. u. Gynäk.*, 1923, **62**, 269) narrates his results in one of the clinics in the Vienna Hospital in the treatment of 50 primaparous patients, near term, who had increased blood-pressure, edema, albuminuria and headache, and 10 cases of eclampsia during labor and 2 postpartum. The entire surface of the body was irradiated, and the source of light is placed about 18 inches from the patient. The treatment is continued twenty minutes for the first day, five minutes upon each of four portions of the body. The duration is increased until pigmentation begins to appear. After this the treatment is given three days weekly and the lessened blood-pressure is taken as a favorable result. The quantity of urine is also measured and when this was a favorable symptom the treatment was increased to ten minutes. Of the 12 eclamptic patients 11 received but one treatment ten minutes in duration. The mammary glands and the vulva were covered with gauze during the treatment, and when the patient was blonde an erythema developed, which in 1 case was followed by the development of small vesicles over an area as large as a small plate; there was no other inconvenience or unfavorable result produced. The blood-pressure of the patient was taken, the patient was given a trial breakfast before the treatment and the quantity of urine carefully measured. It is thought that the treatment produced good by lessening the spasm of the capillary vessels, and that these spasms are largely responsible for the increased blood-pressure.

The Toxemia of Pregnancy.—WINDEYER (*Brit. Med. Jour.*, January 19, 1924) reported the results of 158 cases of eclampsia treated in the Royal Hospital for Women, Sidney, Australia. The mortality rate was 6.96 per cent. In 104 primiparæ there were 3 deaths; in 54 multiparæ, 8. The number of convulsions varied from 1 to 38. The infant mortality was 38 per cent. His experience indicates that when the patient had passed through a toxemic crisis, labor should be induced within a week to secure a living child. The treatment employed was eliminative and the compound jalap powder was freely used, morphin was employed in a considerable percentage of the cases, and veratrone when the convulsions persisted. Where there was persistent cyanosis and pressure of the right side of the heart, bleeding was practised. So far as obstetrical treatment was concerned, the tendency was to interfere as little as possible. The result of treatment has grown better, the writer believes, because the nursing of these patients was better done; there was less obstetrical interference, the convulsions were controlled by reducing blood-pressure until the bowels acted freely and the subcutaneous and intravenous injections of salines is avoided, because the kidneys did not act freely, as a rule, until twenty-four to forty-eight hours after delivery or after the cessation of convulsions.

GYNECOLOGY

UNDER THE CHARGE OF

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Abdominoscopy.—Bearing in mind the invaluable aid which has been rendered to the gynecologist by the various types of endoscopes, especially the cystoscope, it is of considerable interest to direct our attention to the latest member of the endoscope family, the abdominoscope. This instrument devised by STEINER (*Surg., Gynec. and Obst.*, 1924, **38**, 266) resembles the cystoscope and, as the curved end of the cystoscope was found to be very useful, it was made movable. The degree of curvature was regulated by a special mechanism at the opposite end of the instrument. To introduce the instrument with ease, he was careful to regulate the curvature at the end so that it was in the axis of the endoscope. The endoscope has a canal for the introduction of gas similar to the canal used in a cystoscope for irrigation purposes. The air-cock of the endoscope is connected to a bulb similar to that used on a blood-pressure apparatus. A 12-inch rubber tube which connects the air-cock to the bulb is divided by a glass tube which contains sterile cotton for cleaning the gas. A purgative is given the day before the examination and $\frac{1}{4}$ grain of morphin twenty minutes before puncture. The field of puncture is cleansed with benzine and then with alcohol and iodin. Local anesthesia with novocain is used, and it is a good plan to anesthetize also the adjacent peritoneum to prevent sensations during examination. A stab incision is made through the skin and a puncture done with the trocar inserted. Puncture should always be made with the abdominal muscles contracted. Usually there is a reflex contraction, but if none is present the patient is allowed to sit upright. The puncture must be carried out steadily and cautiously and to prevent deep entrance into the abdominal cavity, the trocar should be carefully steadied with the left hand while the abdominal wall is being penetrated. The trocar is removed and the abdominoscope is introduced along the tube which remains in the puncture canal. Then the tube is removed from the puncture canal in order that there may be an air-tight closure. The abdominal cavity is slowly inflated by means of the bulb, the abdominal wall offering very little resistance to the inflation. When the examination is finished the air is allowed to slowly escape, the endoscope is removed and with the hand placed flat on the belly, any remaining air is pressed out. The wound is closed with one suture, swabbed with iodin, and a small dressing applied. Of first importance in performing abdominoscopy is the original position and the correct changes of the position of the patient. As the air is of light specific gravity, it stays uppermost

in the abdominal cavity. Therefore, through changes in position of the patient, we are able to put the air in any place and thus displace the intestines at will. With the patient in a horizontal position, by moderate inflation there is presented a full view of all the organs in their normal relations under the abdominal wall. For an examination of the upper part of the abdomen the thorax is elevated and conversely, for an examination of the pelvis, the pelvis is elevated above the horizontal. For this purpose a safe and easily changeable table is essential. Steiner states that puncture in the lower part of the abdomen with the pelvis greatly elevated shows a beautiful endoscopical picture; in fact, the uterus, tubes, ovaries and sigmoid could have been shown very little better by laparotomy. If carefully performed the puncture is without danger, and there have been no complications observed following the use of this diagnostic procedure. The patients are allowed to get up the next day after the examination.

Relation of the Endometrium to Ovarian Function.—It is the belief of NORRIS and VOGT (*Surg., Gynec. and Obst.*, 1924, **38**, 33) that the endometrium possesses a definite endocrinal function and that this function operates in conjunction with the secretory function of the ovary and is probably subservient to the latter. This theory is at present based only upon physiological and clinical proof. The fact that the endometrium differs histologically from other endocrinal glands is no argument against the theory, since all other endocrinal glands differ one from the other in this respect. They believe that this endocrinal function of the endometrium probably fluctuates with the menstrual cycle, being most active during the premenstrual period. The chief clinical evidence on which this theory is based lies in the established fact that the proportion of women who suffer from nervous phenomena after a hysterectomy with conservation of one or both ovaries is much greater than that of those who exhibit painful or palpable changes in the conserved ovary. The most conclusive evidence is found in those patients who have been treated with radium for the arrest of benign hemorrhages. It is difficult to conceive that in almost every case so treated both ovaries are rendered functionless. Furthermore, there is much experimental evidence that tends to show that in these cases the action of radium is limited to the uterus. The writers are of the opinion that in operations upon the uterus, ovarian conservation is of distinct value, even if panhysterectomy is performed; the ovaries function better, however, and have a longer functional life if a portion of the endometrium can be preserved. The thickened and permanent premenstrual stage of the endometrium, so frequently present in patients suffering from uterine myomata, is the result of stimulation of the endometrium by the presence of the tumor, and accounts for the prolonged bleeding that is often present.

Results of Operation for Retroversion.—In a follow-up study conducted by BLOOMFIELD (*Lancet*, 1924, **206**, 227) to determine the results which are obtained by abdominal operations for uterine retroversion, answers were obtained from 50 patients, of whom 27 attended at hospital for examination and 23 sent written replies only. Ten (20 per cent) expressed themselves as cured, 26 (52 per cent) as relieved, while 14 (28 per cent) remained in *statu quo*. Information as to relief

of individual symptoms has been difficult to obtain, but it is of interest to note that of 25 patients complaining of menorrhagia, relief was obtained in 11; 21 complained of dysmenorrhea, of whom 16 were relieved; of the 41 who had constant pain before the operation 27 were relieved; of 18 patients who complained only of sterility 4 conceived following operation, while 1 of the 3 patients who complained of dyspareunia was relieved. Of the 10 cases who were cured complications were present in 8 cases at operation (80 per cent). In 26 cases who were only relieved complications were present in 21, or approximately 60 per cent; while in the 14 cases who remained the same, only 71 per cent had complications. In the 27 cases who reported for examination the uterus was found anteverted in 22 cases, of whom 12 (55 per cent) were relieved, and retroverted in 5 cases, of whom 3 (60 per cent) were relieved. As a result of this study Bloomfield states that retroversion is not a disease in itself and practically never gives rise to a definite train of symptoms. It is usually complicated by other pathological findings and it is these, as a rule, which indicate operative treatment, and upon which relief of symptoms largely depends. In this series 80 per cent of cured cases were complicated, while only 70 per cent of cases that were unrelieved had complications. Possibly a longer series might show a more marked difference between the two. In cases where no complication is found on clinical examination, and sterility is complained of, operation is sometimes indicated, as closed tubes may be present and a better chance of conception seems to be given after dilatation of the cervix if the uterus is replaced and retained in the anteverted position. In many cases an undoubted nervous element is present, the significance of which must be carefully assessed before operative treatment is undertaken, and in considering the result of such treatment. Too few cases of pregnancy have occurred in this series to enable one to make any statement as to its effect, but from a consideration of the results given by other authors pregnancy does not seem to exert any deleterious effect on orthopedic and clinical results of treatment beyond the fact that it makes prolapsus more common and may, if symptoms recur, transfer the case to the type of retroversion which complicates prolapse, which Bloomfield believes, should not be considered as retroversion, but as prolapse and treated as such.

OPHTHALMOLOGY

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The Clinical Value of Tonometric Measurements.—Bailliart (*Ann. d'ocul.*, 1924, **161**, 81) concludes that tonometry is an acquisition

of great value which it is impossible to dispense with. It is a clinical method, and, like all such methods, it has its advantages and limitations. By its means it is possible to recognize hypertension in cases where the most expert finger is incapable of doing so, of measuring its progress and even, to a certain extent, its gravity. At the same time tonometric figures, except in extreme cases, have no absolute value in themselves; their value is, however, considerable when the measurements are regularly made with the same instrument upon the same patient. It is impossible at present to speak of tension constants in the sense of optical constants, and tonometry does not yet possess the objective value of ophthalmometry. Less attention should be paid to the figures themselves than to the relation with such as may be regarded as normal, or with such as have been found in previous examinations of the same patient. A thermometric curve may be graphed with two different thermometers; that a tonometric curve may be reliable, its elements must be supplied by the same tonometer.

One Hundred Cataract Operations Performed in One Day at Shikarpur, Sind, India.—HOLLAND (*Arch. Ophth.*, 1924, **53**, 155) recounts the circumstances of the clinic and the operations performed by Fisher, of Chicago, upon 113 eyes, January 22, 1923, 13 of which were iridectomies for glaucoma or optical purposes and 100 for cataract, between 10 A.M. and 5.30 P.M., with one hour for lunch, giving six and one-half hours operating, or three hundred and ninety minutes, so that he did one operation every three and a half minutes. The clinic can be best described as an eye camp, lasting for six weeks each year (January 1 to February 15), during which some 8000 cases were dealt with. The wards are just like a large rambling eastern caravanserai, which accommodates about 1000 people. At the busiest time there are between 600 and 800 in-patients and only two English sisters and three ward orderlies as dressers, so that efficient supervision is out of the question, and yet, in spite of the many disadvantages, the end-results are very satisfactory; that year 1322 cataracts were operated upon. One great difficulty is the impossibility of arriving at a true history; the patients and their relatives will often wilfully mislead from fear that if they give a true history operation would be refused; many hopelessly blind patients often declare they have light perception, and often make fairly accurate guesses at counting fingers. Others again have an idea that if they admit light perception they will be rejected because the cataract is not ripe. For this reason several cases each year, surgically perfect, have no vision, and ophthalmoscopical examination reveals various fundus changes, such as retinitis pigmentosa, optic atrophy and so on. Another foe is trachoma, which with all its sequelæ and complications is the rule, and it is exceptional to find an eye free from all traces of this disease. Glaucoma is also extremely prevalent and a large number of the cataract cases have plus tension. This year out of a total of 7800 new out-patients there were 702 cases of glaucoma. The routine method of operating senile cataract is Smith's intracapsular, and the treatment is to dress the eyes of those not complaining, first on the fifth day and on the seventh, if there are no complications, to put on a shade, and the greater number leave on the seventh, eighth and ninth day after operation. Of the 100 cataract operations by Fisher the following immediate com-

plications occurred: Spoon deliveries, 6; burst capsules, 9; vitreous loss, 12; lens in vitreous, 1 (eye bandaged, lens easily removed from anterior chamber third day); expulsion of lens following the incision, 4. After-complications: Prolapse of iris, 3; slight incarceration of the iris in 5. Choroidal hemorrhage occurred in 2 cases; sepsis, 2 cases; hazy cornea, 2 cases; hyalitis, 2 cases; gaping wound, 1 case. Results: Good surgical results in 92 cases; otherwise in 8, of which 2 were due to choroidal hemorrhage, 2 to sepsis, 1 glaucomatous eye which should not have been operated upon and 3 in which there was no vision, probably due to retinal and choroidal changes. If 4 or 5 of the plus tension eyes operated upon had been excluded Dr. Fisher would have had 96 to 98 per cent of surgical successes. Postoperative inflammation is rare and needlings are not required except in a few of the cases of burst capsule.

Papillary Stasis and Decompressive Craniectomy.—Velper (*Rev. d'oto-oculo.*, 1923, **1**, 25) urges that in papillary stasis of intracranial origin, lumbar puncture should always precede any other operative procedure; it should be performed with precaution and repeated with prudence; it should likewise be accompanied by a course of mercury. If, after the expiration of eight or ten days at most, the results are uncertain, trephining should be resorted to without delay; the operation should be done under local anesthesia with the patient seated; the operation should be completed rapidly without exploratory maneuvering. Where precise localization of the lesion is impossible the section should be made in the subtemporal or temporo-parietal region; the dura mater is not to be incised except in cases where the tumor presents at once. The opening in the bone should be from 6 to 8 cm. in diameter. The visual disturbances begin to improve on the second or third day; the visual acuity increases and may become normal in from fifteen to twenty days. As a general rule, the improvement in the visual acuity is maintained; the ophthalmoscopical appearances change more slowly; in some cases several weeks or months are required for the papilla to resume its normal aspect. Slight improvement is always possible, even after complete loss of vision. Following trephining lumbar puncture may be repeated without risk. Definite cure can be obtained when the case is one of serous meningitis or ependymitis, but if tumor be present its evolution is almost never arrested.

Spontaneous Cure of Acute Retrobulbar Neuritis.—Chaillous (*La clin. ophth.*, 1924, **28**, 112) recalls the opinion of some writers that acute retrobulbar neuritis is frequently due to unrecognized sphenoidal sinusitis; they thence conclude that these sinuses should be freely opened in cases of optic neuritis of unknown origin. The writer observes that it has been demonstrated that many cases of retrobulbar neuritis spontaneously tend to complete or almost complete recovery. He recalls four observations which confirm, in this matter, the conclusions of Lenoir and Weill. Hence opening the sphenoidal sinus should not be the rule in retrobulbar neuritis; such intervention should be reserved for cases in which rhinoscopical and radiographical examinations show a lesion of the sinus, or at least to cases of unknown origin in which there is no amelioration at the expiration of some weeks.

The Visual Fields in Empyema of the Nasal Accessory Sinuses in Nasal Anomalies and in Ozena.—Beck and Pillat (*Klin. Monatsbl. f. Augenh.*, 1923, **7**, 78) report examination of the ocular conditions in patients with the above anomalies—a matter bearing directly upon the question of operation in cases of retrobulbar neuritis of uncertain etiology. Of 91 patients with empyema, referred to different ophthalmologists for examination, 6 only showed departure from the normal, all of which, however, were within physiological limits, presenting no signs of retrobulbar neuritis. The authors next extended their researches to nasal anomalies, it having been supposed that certain varieties were a disposition to retrobulbar neuritis. The material examined included 47 patients with normal nasal conditions, 53 with empyema of a single accessory sinus, 64 with nasal anomalies and 25 with ozena. Of the first group 4 showed contractions or indications of scotoma; these would have been regarded as pathological in the presence of disease of the accessory sinuses. Of the second group, the empyemata, 6 showed departures from the normal, *i. e.*, contractions of the field in 3, enlargement of the blind spot in 3; central scotoma was found in none of the cases. The third group, anatomical anomalies of the nose, presented 5 abnormal findings, of which 1, a tabetic with retrobulbar neuritis, is to be excluded; the remainder showed enlargement of the blind spot, central scotomata and slight contraction of the field. Of the cases with ozena 2 only presented departures from the normal, 1 (positive Wassermann) left-sided contraction for red, the second slight enlargement of the blind spot for blue alone. The authors conclude from their researches that neither in empyemata nor in ozena, nor in gross anomalies of the nose are ocular changes found which can be referred with certainty to a retrobulbar neuritis. The question, therefore, arises whether in apparently normal conditions of the sinuses, when retrobulbar neuritis is present which has proved refractory to other therapeutic measures, it is justifiable to practice opening of the sinuses, especially where conditions in the nose are normal. This question must be answered positively, in as much as the danger of such interference is slight.

PATHOLOGY AND BACTERIOLOGY

UNDER THE CHARGE OF

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A Comparison of the Ziehl-Neelson and Schulte-Tigges Methods of Staining Bacilli.—Having been impressed with the fact that many patients who exhibited signs of pulmonary tuberculosis gave a nega-

tive test for tubercle bacilli, SCHOUB (*Jour. Bacteriol.*, 1923, **8**, 121) applied several different methods of staining in the hope of finding a more efficient procedure than the Ziehl-Neelson technic. After numerous endeavors it was found that the Schulte-Tigges method gave a higher percentage of positives. This method consists in flooding the heat-fixed slide with carbolfuchsin (10 cc of saturated solution of basic fuchsin in 95 per cent of alcohol and 90 cc of 5 per cent carbolic acid); heating the slide to steaming for one minute; washing off the excess stain with tap water and decolorizing with 10 per cent aqueous solution of sodium sulphite; washing thoroughly with tap water and counterstaining with a saturated solution of picric acid; washing with tap water, drying and examining. The tubercle bacilli are red and the background is pinkish-yellow. Parallel observations were conducted on 800 sputums, 244 of which were positive with the new stain and 183 with Ziehl-Neelson. No sputum was ever found positive with the Ziehl-Neelson method and negative with the new method, while the reverse was true in 33 per cent of the tests. In addition, by actual count of the bacilli in the various preparations, the new method revealed five times as many organisms as the Ziehl-Neelson. The author does not believe that his results corroborate the opinion of some—that all tubercle bacilli are acid-fast. He further attributes the success of the new stain partly to the counterstain (picric acid), but more especially to the decolorizer (sodium sulphite), which also clarifies the slide, consequently exposing more organisms. He concludes that the Schulte-Tigges method is easier than the Ziehl-Neelson, that it gives about 33 per cent more positives, that it exposes more than five times more organisms and that it abolishes the use of alcohol as a decolorizer.

The Vaccine Treatment of Asthma.—RACKEMANN and GRAHAM (*Jour. Immunol.*, 1923, **8**, 295) reported 131 cases which received autogenous and stock vaccines for such conditions as chronic pulmonary emphysema, chronic cough, and asthma without emphysema. The autogenous vaccine consisted of twenty-four-hour dextrose broth cultures of organisms which were fished from the second blood-agar plate which has been inoculated with bacteria recovered from the original blood-agar plate on which the sputum had been spread. These organisms were washed three times in salt solution containing 0.5 per cent carbolic acid and killed by heating at 56° C. for one hour. Each cubic centimeter contained about 2,000,000,000 organisms but there was no attempt at accurate standardization. The autogenous vaccines were injected intradermally employing equal doses of the various bacteria and the one producing the greatest degree of local redness and swelling was selected for treatment. The initial dose was about 0.25 cc and was administered at intervals of five to seven days depending on the local reaction and was continued until a dose of 2,000,000,000 organisms was reached or until clinical improvement had been established. Treatment was abandoned if six good-sized doses failed to produce improvement or local reactions. Successful results occured in those cases in which inoculations gave considerable local reaction. Four cases, however, showed improvement without local signs. The importance of local reaction plus the fact that the results with stock

vaccines were as good or better than those with autogenous vaccines led the authors to believe that the action of oil vaccines in asthma was non-specific. Of the entire series of 131 patients, 9 or 7 per cent were cured; 31, or 22 per cent were definitely benefited; 13, or 10 per cent were helped somewhat; 24, or 18.5 per cent were relieved temporarily and 54 or 41 per cent did not respond in any way.

Effect of Spices on Growth of Clostridium Botulinum.—Following a previous study on the effect of spices on the growth of various aërobic bacteria, BACHMANN (*Jour. Infect. Dis.*, 1923, **33**, 236) investigated the action of such spices as cloves, cinnamon, allspice, ginger, nutmeg, cayenne pepper, white mustard and black mustard on 6 strains of Clostridium botulinum, derived from different sources, which were known to be capable of growing in mince meat. No inhibition of growth was found in 1 and 2 per cent of spice, but there was some retardation with allspice and cloves when 2.5 per cent was used. The bacteria formed toxin in the presence of this amount of spice. The author concluded that "spices as used in flavoring foods do not help to make the food safe if there is contamination with Clostridium botulinum" and admonishes that "for safety such foods as mince meat should be unquestionably sterilized or else heated to the boiling point before they are tasted."

Chemotherapy of Experimental Typhoid Carrier Condition.—Although numerous attempts both clinical and experimental have been made to sterilize the focus of infection in the typhoid carrier, the results have not been satisfactory. Having previously shown (*Jour. Infect. Dis.*, 1921, **29**, 495) that a dyestuff of the triphenylmethane series, new fast green 3 B, had a certain value for clearing up rabbits experimentally infected with Bacillus typhosus, but also that embolic deaths occasionally occurred, BECKWITH (*Jour. Infect. Dis.*, 1923, **33**, 457) continued his attempts to sterilize gall-bladders of experimental rabbits by various other chemicals. Accordingly, arsphenamin, neoarsphenamin, iodin and many acid dyestuffs were injected intravenously following the inoculation of typhoid bacilli into the gall-bladder. The dyestuffs were utilized in 0.5 per cent distilled water solutions. It was found that none of these were effective in eradicating the experimentally produced carrier state, although certain temporary changes in the growth habit of Bacillus typhosus were encountered as a result of intravenous injection of particular dyestuffs.

The Effect of Peptone on the Peripheral Circulation.—In studying what factors other than the influence of the large mass of smooth muscle in the hepatic veins of the dog has on the fall in arterial pressure in anaphylactic and peptone shock, SIMONDS and RANSON (*Jour. Exper. Med.*, 1923, **38**, 275) injected peptone solution into the iliac circulation of 7 dogs and horse serum into 1 sensitized dog. The peptone was inoculated into the left iliac artery by introducing it into the severed right iliac artery, so that the conditions of experimentation permitted of a normal blood supply in a normal manner. The effect was noted by recording the changes in leg volume by means of a plethysmograph and the carotid blood-pressure was taken with a mercury manometer, both instruments writing on the same kymograph. It

was found that injection of the peptone solution directly into the artery of the leg of a dog was followed by an abrupt increase in leg volume, which was of short duration and was followed quickly, usually in less than one-half minute, by a decrease in the volume of the limb below that previous to the injection. The phases of the leg volume curve bore a fairly definite relation to the changes in arterial pressure. The authors believe that their results indicate "That the long-continued low arterial pressure in peptone shock, and probably in anaphylactic shock, may be hastened but is not maintained by peripheral dilatation, and suggest that there is an impounding of the blood in some other part of the body."

Iodin Metabolism on Normal Diet in Relation to Prevention of Goiter.—McCLENDON and HATHAWAY (*Proc. Soc. Exper. Biol. and Med.*, 1923, **21**, 129) call attention to the fact that "It would require two thousand years to drink enough Lake Superior water to accumulate 20 mg. of iodin, and since the normal adult thyroid contains about this quantity and at least 50 per cent of persons drinking this or similar water escape goiter, there must be iodin in foods." They found that a man living in a moderately goitrous region (Minneapolis), consumed 0.057 mg. of iodin in three days on a normal diet, and excreted 0.021 mg. of iodin during the same period, having retained 0.036 mg. of iodin in three days. At this rate it would require about five years to accumulate 20 mg. of iodin. From tables they give, the authors show that persons eating much roughage (wheat, peeled and cored apples, oats, spinach and string beans) and drinking considerable quantities of milk of herbivorous animals would be immune to goiter.

The Acid-base Balance in Pneumonia.—While studying the respiratory and metabolic disturbances occurring in pneumonia, HASTINGS, NEILL, MORGAN and BINGER (*Proc. Soc. Exper. Biol. and Med.*, 1923, **21**, 66) determined the acid-base balance and the arterial oxygen unsaturation of pneumonia patients. Thirty observations made on 16 patients, indicated that almost all of the points, as plotted on the Van Slyke acid-base diagram, so modified as to include iso-CO_2 tension lines, were well within the normal acid-base area. In no instance was an uncompensated acidosis encountered, nor were there any cases of sufficient severity to indicate bicarbonate therapy. In 8 instances, in which repeated observations of the acid-base condition of the same patients were made, it was found that during the febrile period the CO_2 tension tended to be lower and the pH higher than after the temperature had returned to normal. The authors state that these results "Indicate that during the febrile period there is overstimulation of the respiratory mechanism which leads to a lower CO_2 tension and a slightly higher pH, but that this disturbance does not usually remove the patient from a normal acid-base condition." No direct relation between the degree of oxygen unsaturation and the low CO_2 tension of the febrile period was found.

HYGIENE AND PUBLIC HEALTH

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Chronic Carbon Monoxide Poisoning.—EGDAHL (*Jour. Am. Med. Assn.*, 1923, **81**, 281) states that chronic carbon monoxide poisoning, although recognized for a long time, has not been given the attention it deserves by the medical profession. As the chances for exposure to carbon monoxide are so great, it would be well for the physician to keep in mind the possibility of chronic poisoning when a patient presents himself with ill-defined symptoms which cannot be explained otherwise. Repeated exposures to carbon monoxide, but not in sufficient degree to cause acute poisoning, will cause symptoms similar to the results of fatigue, and can be explained by lowered amount of oxygen in the blood. Just as a state of continued fatigue, so will a state of chronic carbon monoxide poisoning lower the resistance to various infections, or favor renewed activity of an old process. When there is a possibility of exposure to carbon monoxide, it would be well to make a blood test. By the use of various simple laboratory tests, it is possible to diagnose an early, or a presymptomatic stage of chronic poisoning and ward off the possibility of serious results. Preventive medicine has here a new field. Carbon monoxide poisoning is no longer confined to certain industries: the chances for poisoning are universal.

Effect of Acidification on Toxicity of B. Botulinus Toxin.—GEIGER and GOUWENS (*Pub. Health Reports*, 1923, **38**, 2249) discuss previous work showing that acidification increases the toxicity; they describe their own experiments and present the following summary and conclusions: (1) Toxins of four strains of Bacillus botulinus were not increased in potency at any hydrogen-ion concentration, regardless of the length of time of exposure. The acid mixtures employed in this study were hydrochloric acid-sodium citrate and acetic acid-sodium acetate mixtures; (2) the injection of 1 cc of a buffered acetic acid of pH 4.0 causes the death of mice; this occurs whether Bacillus botulinus toxin is present or absent; with greater concentration of the hydrogen ions, death is more rapid, and less than 1 cc is sufficient to cause death in twenty four hours; (3) hydrochloric acid-sodium citrate, hydrochloric acid-potassium acid phthalate, and lactic acid-calcium lactate mixtures between the limits pH 4.0 and 2.3 do not kill white mice when injected intraperitoneally in 1 cc amounts. The acetic acid therefore appears to have a selective action upon white mice. This is not due to the acetate ions or undissociated sodium acetate molecules alone.

Child Mortality with Reference to the Higher Education of Parents.—Lennox (*Am. Jour. Hyg.*, 1924, **4**, 52) has tabulated statistics from a group of 939 families, reporting 2475 pregnancies, with reference to the medical and general education of parents. He states that families in which the father is a doctor do not have lower mortality rates among children than the other professional or business groups. The small group of doctors engaged in a specialty show unusually high rates. Miscarriage rates for doctors' wives are high, probably because reports from other occupational groups are falsely low. College attendance of a parent or extended years of schooling is accompanied by slightly higher mortality rates of children. In case both parents have attended college or had extended schooling, there is a slightly lowered mortality rate. A disproportionate number of children whose parents have had less than a grammar school education have died of infectious diseases. The more highly educated parents report a larger proportion of living children who are in robust health. The above conclusions apply to a comparatively small group of persons. The question raised is of sufficient importance to warrant securing further evidence from much larger groups in various sections of the country.

Studies in Cancer.—Burrows (*Proc. Soc. Exper. Biol. and Med.*, 1923, **21**, 82) reports the results of his investigations on: The effect of circulation on the functional activity, migration and growth of tissue cells; the significance of the effect of circulation on the growth of cells; cellular growth and degeneration in the organism; factors regulating the production of cancer in the organism. He states, in conclusion, that cancer may be the normal outcome of any substance or condition capable of building a densely cellular tissue in the organism associated with an orderly decrease in the blood supply. It is not the result of any primary changes in the cell but to a specific rearrangement of cells, intracellular substances and bloodvessels in the organism.

Studies on Typhus Virus in the Louse.—Breinl (*Jour. Infect. Dis.*, 1924, **34**, 1) found it possible to pass the typhus virus from louse to louse repeatedly with Weigl's method of injection. The course of the disease after injection of emulsified louse intestines differs from that after injection with virulent guinea-pig brain in those points: (*a*) In the guinea-pig the period of latency is generally much shorter; often the fever is abridged or interrupted by periods of normal temperature, and the height of the fever curve is less than after infection with guinea-pig virus; some animals die of the infection. (*b*) The agglutinin for the strain used appears much sooner in the rabbit after injection of louse virus; as a rule, the half of the maximal titer is reached on the seventh day. Production of agglutinin and active immunity can also be obtained in the rabbit by injecting emulsified louse intestines, to which phenol has been added. Guinea-pigs can be immunized also by repeated treatment with dead louse virus. The peculiarities of the infection following the injection of the louse virus are explained by the coëxistence of dead and living virus. The typhus virus multiplies considerably within the louse, but does not become more virulent. Ten days after infection the intestines of a louse contain 100 doses of living virus. The body of the louse contains only small quantities

of virus after the intestines have been removed. From this fact we can draw conclusions as to the way of natural infection in man. Lice fed on a patient one day after the fever had disappeared proved to be infectious seven days later. It is possible to infect lice with an emulsion of virulent guinea-pig brain.

The Cultivation of the Microörganisms of Rocky Mountain Spotted Fever (Dermacentroxenus Rickettsi) and of Typhus (Rickettsia Prowazeki) in Tissue Plasma Cultures.—WOLBACH and SCHLESINGER (*Jour. Med. Res.*, 1923, **44**, 231) state that the virus of Rocky Mountain spotted fever and the virus of typhus survive in tissue-plasma cultures for a length of time corresponding to the survival of the endothelial cells multiplying in the cultures. The survival of the virus may be extended by "subcultures," a procedure which involves the washing of the tissue in Ringer's solution, and the addition of fresh plasma in order to permit the continuation of growth of the tissue cells. In both instances the microörganisms associated with the two diseases appeared in endothelial cells in the tissue cultures, in such numbers as to admit of no other explanation than that of multiplication. In the case of Rocky Mountain spotted fever a filamentous form appeared in the cultures in addition to forms previously described in arachnoid and mammalian tissues. In the case of typhus, coccoid, bacillary and filamentous forms appeared in exact duplication of the morphology of Rickettsia prowazeki, as described in lice infected with typhus.

Methods of Administering Iodin for Prophylaxis of Endemic Goiter.—OLESON (*U. S. Pub. Health Repts.*, 1924, **39**, 45) reviews briefly the iodin prophylaxis in goiter. Reference is made to administration by inhalation and external application, but it is pointed out that internal administration is the most satisfactory means. Various forms of oral administration are referred to and the favorable results from chocolate tablets containing sodium iodide are especially noted. Iodized table salt is also referred to as well as iodized drinking water, but both are regarded as in the experimental stage. The possible disadvantages of rather indiscriminate iodin medication are mentioned. The author believes that in goitrous areas both boys and girls should receive the prophylactic and that the administration should be begin as early as eight years of age.

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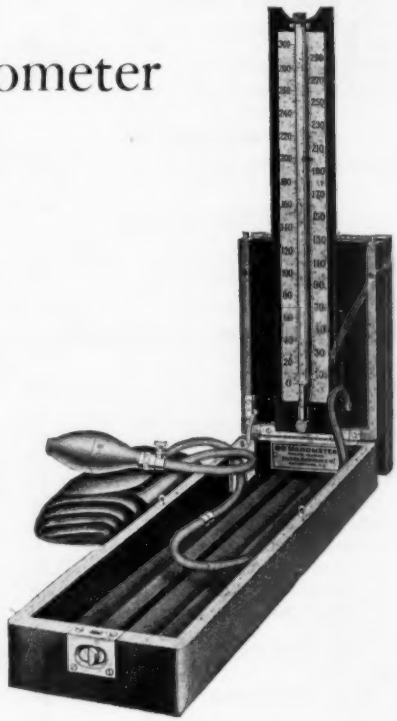

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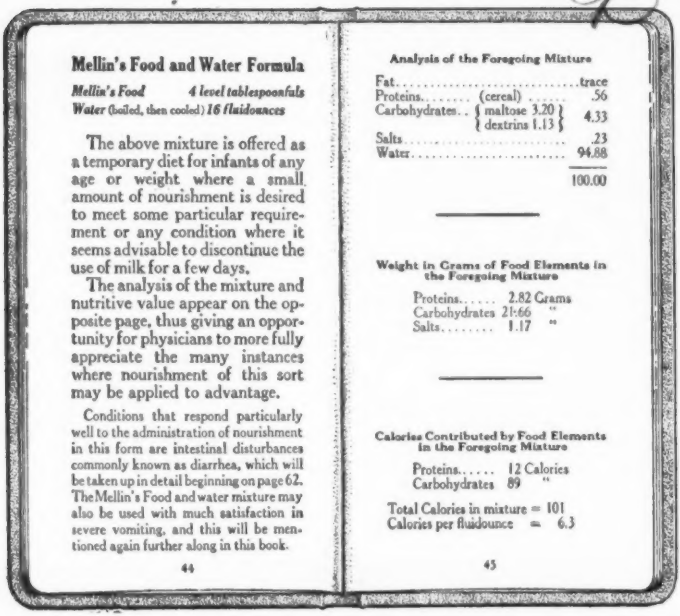

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